Different perspectives on psoriasis care with biologics:

to explore, to compare, and to predict treatment outcome with biologics in psoriasis

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Different perspectives on psoriasis care with biologics:

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Contents

Abbreviations

ADA:	Adalimumab
AEs:	Adverse Events
BioCAPTURE:	Continuous Assessment of Psoriasis Treatment Use Registry with Biologics
BMI:	Body Mass Index
BSA:	Body Surface Area
CI:	Confidence Interval
CyA:	Cyclosporine
DLQI:	Dermatology Life Quality Index
EMA:	European Medicine Agency
ETA:	Etanercept
FAE:	Fumaric Acid Esters
GEE:	Generalized Estimating Equation
GRADE:	Grading of Recommendations Assessment, Development and Evaluation
HLA:	Human Leukocyte Antigen
HR:	Hazard Ratio
IgG1:	Immunoglobulin G1
IL:	Interleukin
IQR:	Inter-Quartile Range
LCE:	Late Cornified Envelope
LTBI:	Latent Tuberculosis Infection
MCR-DS:	Multivariate Cox Regression analysis for Drug Survival
MCR-P:	Multivariate Cox Regression analysis for Predictors
MLRA:	Multilevel Linear Regression Analysis
MTX:	Methotrexate
NT:	Acitretin (Neotigason)
OIS:	Optimal Information Size
PASI:	Psoriasis Area and Severity Index
PASI≤5:	Absolute PASI score is equal to or less than 5
PASI50:	50% reduction in PASI score
PASI75:	75% reduction in PASI score
PASI90:	90% reduction in PASI score
PASI100:	100% reduction in PASI score, i.e. the absolute PASI score is zero
PGA / PhGA:	Physician's Global Assessment
PROMs:	Patient Reported Outcome Measures
PSORS1:	Psoriasis susceptibility 1
PUVA:	8-methoxyPsoralen-UltraVioletA
QoL:	Quality of Life
RCT:	Randomized Controlled Trial
RRR:	Relative Risk Ratio
SAEs:	Serious Adverse Events
SD:	Standard Deviation
TB:	Tuberculosis
TEs:	Treatment Episodes
TNF:	Tumor Necrosis Factor
TNFAIP3:	Tumor Necrosis Factor Alpha-Induces Protein 3
TNF-RII:	Tumor Necrosis Factor – Receptor II
USTE:	Ustekinumab
UV:	Ultraviolet

Introduction to thesis

Since 2005, the Department of Dermatology at the Radboud university medical center Nijmegen, established a prospective registry called BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics). Patient and treatment characteristics as well as patient reported outcomes of all consecutive patients with psoriasis that are being treated with biologics, i.e. agents derived from living organisms, are being registered. From 2010, large regional hospitals have been participating in BioCAPTURE. At the moment, nine regional centers contribute to BioCAPTURE. The goals of the BioCAPTURE registry are to gather data on the long-term effectiveness, drug survival and safety of biologics in patients with psoriasis, as well as collecting patient reported outcome measures (PROMs). Over the past eleven years, several research questions have been answered using data from BioCAPTURE. This thesis contains data from the literature summarized in (systematic) reviews and data from the BioCAPTURE registry. The focus of this thesis will be on the long-term effectiveness and drug survival of biologics in patients with psoriasis as well as providing complementary data for current guidelines. Before disclosing our formulated research questions, the reader will first be provided with an overview of psoriasis as a disease entity in the first chapter and its treatment options in the second chapter of this thesis. In the third chapter, the three main sections of this thesis (i.e., effectiveness, drug survival and improvements of effectiveness/efficacy) will be shortly addressed, followed by the research questions in chapter 4. Chapters 5-12 include original articles based on the formulated research questions. The answers to the research questions will be summarized and discussed in chapters 13 (English) and 14 (Dutch).

PART I

GENERAL INTRODUCTION

1

Overview of psoriasis

1.1 Introduction to psoriasis

Psoriasis is a chronic, immune-mediated, polygenic, inflammatory skin disease.[1,2] Psoriasis is common, with a prevalence of 2-3% in Europe and North America and it results in a major economic burden with an annual cost of approximately $ 112 billion in the United States in 2013.[2-4] Different forms of psoriasis exist, of which chronic plaque type psoriasis, i.e. psoriasis vulgaris, represents the most common form of psoriasis with approximately 90% of patients with psoriasis affected by it.[2] In this thesis the term "psoriasis" indicates chronic plaque type psoriasis, unless stated otherwise. Psoriasis has an immense impact on the physical, emotional and social well-being of patients with this skin disease.[5] It impairs quality of life as much as other chronic diseases such as cancer, diabetes and heart disease.[6] Covered with sharply demarcated, erythematous, silvery scaly plaques, patients with psoriasis have been stigmatized and even rejected from society.[7,8] Recently performed studies show that patients with psoriasis are still stigmatized and that sexual difficulties are experienced amongst male and female patients.[9-11] Extensive research into the pathogenesis of psoriasis eventually led to astonishing new therapeutic options for patients with this life-altering disease.

1.2 History of psoriasis

Going back in time, psoriasis probably already existed more than 2000 years ago.[12] Throughout history different words have been suggested and used for psoriasis. The Term 'Zaraath' in the bible could have been used for the psoriasis that we know today.[13] However, uncertainty exists since this term could have also been used to describe many other skin diseases, e.g. leprosy, eczema and/or scabies.[12,14] Hippocrates (460-377 B.C.), in his Corpus Hippocraticum, used 'psora' for the first time, which means 'to itch' in Greek, but probably used it for another disease entity than psoriasis.[8,15] The first clinical description of psoriasis stems from Aurelius Cornelius Celsus (± 25 B.C. – 45 A.D.), although he used the term 'impetigo' to describe this skin disease.[8] The first physician to use the term psoriasis was Galen (± 133-200 A.D.). Robert Willan (1757-1812), of Yorkshire[16], was the first to accurately describe psoriasis in 1808, but called it 'lepra'.[12,14,17] Austrian physician Ferdinand von Hebra was the first to distinguish leprosy from psoriasis in 1841.[8] In a congress in 1946, it was suggested to use "rosa plateada" (silvered rose) instead of psoriasis.[14] Psoriasis, however, remained the world-wide adopted term.

1.3 Epidemiology of psoriasis

The prevalence of psoriasis is estimated to be 2-3% in European countries and in North America.[2,3,18] In non-Caucasian populations, prevalence seems to be lower with a prevalence rate of less than 0.5% in certain African countries, China and Japan.[19-21] Epidemiological research indicates that countries closer to the equator have lower prevalence rates compared with countries more distant from it.[21] Psoriasis is equally distributed between men and women.[3] Male patients, however, may have more severe psoriasis compared with female patients, which explains the higher proportion of men being treated with biologics.[22] On the other hand, female patients might have psoriasis at an earlier age than male patients.[23,24] The age of onset of psoriasis shows a bimodal distribution with peaks at 16-22 years and 57-60 years of age.[25] More than half of patients with psoriasis develop their skin lesions before the age of 40 years and approximately 75% of patients before the age of 46.[3,26]

1.4 Histological features and clinical correlation

In psoriasis, the mitotic activity of basal keratinocytes is increased with keratinocytes moving from the basal layer to the cornified layer within one week instead of the normal one month period.[1] Histopathological changes in the epidermis of the psoriasis lesions include acanthosis (thickening of the viable layers), elongation of the rede ridges, loss of the granular layer, hyperkeratosis (thickened stratum corneum), and parakeratosis (nuclei in the stratum corneum). These features correspond with thickening and scaling of the skin of patients with psoriasis.[1,2,7] In the dermis, blood vessels increase in number and become dilated. These contorted capillaries reach into the tips of the dermal papillae and are responsible for the redness of psoriasis lesions.[2,7] In both the epidermis and dermis, an infiltrate of leukocytes can be seen with dendritic cells, T-lymphocytes, macrophages and neutrophils.[1,2,7] Neutrophilic granulocytes accumulate within the epidermis to form the pustules of Kogoj or subcorneal to form Munro's microabcesses.[2]

1.5 The natural course of psoriasis

In untreated individuals that are prone to developing psoriasis, psoriatic lesions may erupt due to external or internal triggering factors.[7] Once the psoriasis has surfaced, lesions may develop locally or more widespread.[2] Small pinpoint lesions indicate the start of new psoriasis lesions.[26] Psoriatic lesions may occur at any site of the body, but are usually seen at the extensor sites of arms and legs (i.e., elbows and knees)

and on the head and buttocks.[26,27] Unfortunately, psoriasis is a skin disease for which a complete cure is still absent; once psoriasis surfaces it is a lifelong disease.[26] During the natural course of this disease, the size and/or number of skin lesions may increase or decrease or all lesions may disappear completely (complete remission, although mostly temporarily).[17] In one study, in which 5600 patients with psoriasis were followed, 39% achieved complete remission over a long period of time (years).[28] After complete remission, patients may experience recurrence of disease. It is still impossible to accurately predict a patient's clinical course.[29,30] Patients with an early onset of psoriasis (15-25 years of age) more often have a first degree relative affected by psoriasis and usually develop a psoriasis that is more unstable with frequent relapses when compared with patients with psoriasis with a late onset of disease (60-70 years of age).[25] Women who become pregnant usually experience an improvement of psoriasis (40-60% of pregnant patients), most of them within the first trimester and less within the second.[31,32] In about 10-20% of pregnant woman the psoriasis deteriorates.[31] Breastfeeding has probably no significant effect on psoriasis.[32]

1.6 Factors triggering psoriasis

Genetic susceptibility together with external or internal triggering factors and cells from the immune system play a role in the pathogenesis of psoriasis. Factors that may trigger psoriasis include smoking, stress, skin trauma (i.e. Koebner phenomenon. Also ultraviolet (UV) radiation, i.e. sunburn), infections (e.g. streptococcal throat infection), alcohol use and certain drugs such as antimalarials, ß-blockers, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, lithium and imiquimod.[33-36] Weight is a factor that seems to have an influence on psoriasis severity.[33,37]

1.7 Immunopathogenesis of psoriasis

Extensive research has been conducted in elucidating the role of the immune system. Current evidence shows a dysregulation of the immune system in patients with psoriasis (Figure 1). The immune system can be subdivided into the innate immune system which immediately protects the human body from microorganisms and the adaptive immune system which forms the second line of protection, is more slowly activated and has a memory function.[38] The link between the innate and adaptive immunity is constituted by the dendritic cell.[7] Keratinocytes, macrophages and natural killer T-cells belong to the innate immune system.[39] Keratinocytes constitute

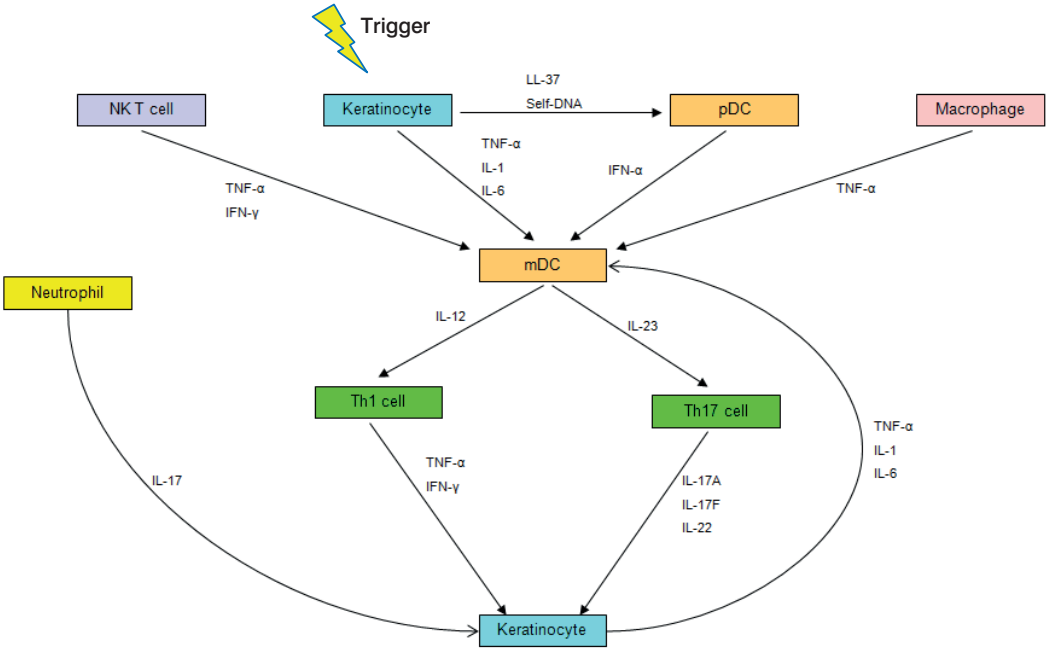
about 95% of cells of the epidermis. They contain the antimicrobial peptide cathelicidin (LL-37) in order to prevent microbial infection.[40] It is hypothesized that environmental factors and genes, in predisposed individuals, may cause keratinocytes to become stressed or even damaged. Consequently, these stressed or damaged keratinocytes may release LL-37 and self-DNA, which form complexes.[2,7,40,41] As a result, nucleases will be unable to degrade self-DNA.[41] Plasmacytoid dendritic cells will capture these newly formed LL-37/self-DNA complexes through endocytoses.[40] Then, self-DNA will interact with toll-like receptor 9, which lies intracellular within the plasmacytoid dendritic cells, and will cause these dendritic cells to produce interferon-α, a cytokine of the innate immune system.[40,41] In psoriasis, keratinocytes also release their own pro-inflammatory cytokines (interleukin (IL)-1, IL-6 and tumor necrosis factor(TNF)- α).[7] Natural killer T-cells and macrophages contribute to the innate immune response by releasing TNF-α and interferon-γ. Interferon-α, TNF-α, interferon-γ, IL-1 and IL-6 will activate myeloid dendritic cells.[2,7] These cells will then travel to nearby lymph nodes and produce IL-12 and IL-23 in order to stimulate the formation of T-helper 1 cells and T-helper 17 cells, respectively, from naive T cells.[7] These helper T-cells of the adaptive immune system will produce the cytokines TNF-α, interferon-γ, IL-17 and IL-22 (Figure 1). Hereby, they will stimulate the proliferation of keratinocytes and will maintain them in a stressful state. As this circle of cytokine release continues, patients will start to develop psoriatic lesions.[1,2,7] Recent research has shown that neutrophils, by producing IL-17, also stimulate keratinocytes into uncontrolled cell division and secretion of cytokines.[42]

1.8 Genetic susceptibility to psoriasis

Genes have been found to play a role in the development and severity of psoriasis.[1] The risk that an individual might develop psoriasis is 14-30% if one parent is affected and 41-75% if both parents are affected by psoriasis.[1,3,31,32] In concordant monozygotic twins the age of onset, severity, distribution pattern and the course of psoriasis appear to be similar when compared with concordant dizygotic twins.[43,44] Many different susceptibility loci for psoriasis have been identified with genome-wide linkage studies and genome-wide association studies.[43] Susceptibility loci have been found related to the adaptive and innate immunity as well as to the skin barrier function.[30,45] The most important locus and replicated in almost all linkage studies is psoriasis susceptibility 1 (PSORS1); a locus in the major-histocompatibility-complex region on chromosome 6.[3,30] PSORS1 accounts for 35-50% of the heritability of psoriasis.[3,45] The human leukocyte antigen (HLA)-Cw6 gene is the strongest susceptibility allele of the PSORS1 locus to early onset psoriasis and guttate psoriasis.[30,45,46] In the patients with early onset psoriasis (≤40 years of age) about

78% were HLA-Cw6 positive, compared with only ~37% in patients with late onset psoriasis (>40 years of age).[25] Of the patients that were HLA-Cw6 positive, approximately 85% of patients had early onset psoriasis.[25] Patients with an early onset of disease more often experienced a more severe psoriasis compared with patients with a late onset of disease.[25] Smoking might play an important role in the development of psoriasis as it enhances the expression of genes like HLA-Cw6.[34] An example of psoriasis associated-genes involved in the innate immunity and skin barrier integrity is, respectively, tumor necrosis factor alpha-induced protein 3 (TNFAIP3) gene and the late cornified envelope (LCE) gene cluster.[47]

Figure 1 Schematic overview of the immunopathogenesis of psoriasis



Legend:
NK T cell: Natural killer T cell | pDC: plasmacytoid dendritic cell | mDC: myeloid dendritic cell
LL-37: cathelicidin | IFN: interferon | IL: interleukin | TNF: tumor necrosis factor | Th: T helper cell

Figure is partly based on Figure 2 from Nestle, et al.[7]

1.9 Psoriasis and comorbidities

Psoriasis is associated with several comorbidities, including psoriatic arthritis, cardiovascular disease, Crohn's disease, diabetes mellitus (mainly type 2), metabolic syndrome (hypertension, obesity, glucose intolerance, dyslipidemia), alexithymia, anxiety and depression, cancer (e.g., lymphoma and non-melanoma skin cancer) and obstructive sleep apnea.[2,3,48-51] Dermatologists should be aware of these associations when treating their patients with psoriasis. Although psoriasis is linked to these comorbidities, some comorbidities may be the consequence of certain treatments (e.g., photochemotherapy resulting in non-melanoma skin cancer) or patient behaviour instead of a true relation with the skin disease itself.[52,53]

1.10 Psoriasis and quality of life

The quality of life of patients with psoriasis is severely affected by their skin disease.[2,54] The quality of life of patients with psoriasis is usually measured with the Dermatology Life Quality Index (DLQI) questionnaire, although at least 20 other questionnaires exist.[55,56] The DLQI is a validated, 10-item questionnaire and results in a score between 0 and 30. A lower score represents a better quality of life (DLQI of 0-1: no effect; DLQI of 2-5: a small effect; DLQI 6-10: a moderate effect; DLQI 11-20: a very large effect; DLQI 21-30: an extremely large effect on my life).[57] Interestingly, not only the quality of life of patients with psoriasis is affected, but also the quality of life of persons living with these patients.[58]

1.11 Measuring severity of psoriasis

The severity of psoriasis can be measured with at least 53 different measures of which the Psoriasis Area and Severity Index (PASI), Physician's Global Assessment (PGA) and Body Surface Area (BSA) are widely used in randomized controlled trials (RCTs) and daily clinical practice.[59-61] Of these, the PASI score is considered the most important outcome measure. The PASI score ranges from 0-72, with a higher score reflecting a more severe psoriasis.[62] The PASI score is calculated as follows: $0.1(E_H + I_H + D_H)A_H + 0.2(E_U + I_U + D_U)A_U + 0.3(E_T + I_T + D_T)A_T + 0.4(E_L + I_L + D_L)A_L$, with E= erythema (0: absent – 4: very severe), I= induration (0: absent – 4: very severe), D= desquamation (0: absent – 4: very severe), H= head, U= upper extremities, T= trunk, L= lower extremities and A= body surface area that is affected by psoriasis (0 = no involvement; 1= <10%; 2= 10-29%; 3= 30-49%; 4= 50-69%; 5= 70-89% and 6= 90-100% of body surface area affected).[62,63] There is no consensus on how

to interpret the PASI score, but moderate to severe psoriasis is usually a PASI≥10.[64] The "rule of tens" suggests that moderate to severe psoriasis is an absolute PASI score of ≥10 or a BSA score of ≥10 or a DLQI score of ≥10.[65] In RCTs, the improvement in PASI score compared with baseline PASI score is often used in order to express the efficacy of the studied agent.[66] A PASI75 indicates a 75% improvement when compared with baseline PASI score. A PASI75 of 60% at 16 weeks of treatment means that 60% of patients achieved a 75% improvement in PASI score when compared with baseline PASI score at 16 weeks of treatment.[62] The PGA is scored by the dermatologist and might range from 0-5, 0-6 or 0-7 (no psoriasis – very severe psoriasis), depending on the PGA used.[59] The BSA is the percentage of body surface area that is affected by psoriasis (0-100%).

2

Treatment of psoriasis

2.1 Introduction to the treatment of psoriasis

Psoriasis can be treated with topical treatments, phototherapy, conventional systemic agents, biologics and more recently small molecules.[67,68] The course of psoriasis is different between individuals and therefore psoriasis treatment is patient-centered.[69,70] Many different factors play a role in choosing the appropriate therapy, such as the form, location and extent of psoriasis, the patient's quality of life, comorbidities, (future) pregnancy wish, work and hobbies, patient preferences, as well as costs of psoriasis treatment.[69,71] Patient adherence to therapy is one of the challenges a dermatologist faces when treating patients with psoriasis. By explaining the therapeutic options and respecting patient preferences, the dermatologist is offered an opportunity to build the patient-doctor relationship which is one of the important factors that can increase patient adherence to the antipsoriatic therapy. Other factors improving patient adherence include treatment satisfaction and satisfaction with the quality of care.[72] The limited evidence available suggests that patient adherence is highest for biologics, followed by oral systemic therapies, phototherapy and lastly topical therapies.[72]

2.2 Topical therapies

The efficacy of topical therapies for plaque psoriasis has been studied in RCTs.[73] Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are of limited effect for psoriasis of the body, but might be used for facial, flexural and genital psoriasis.[67] For psoriasis of the body, very potent corticosteroids (e.g., clobetasol proprionate), potent corticosteroids (e.g., bethametasone dipropionate), potent corticosteroids combined with vitamin D analogues (e.g., betametasone dipropionate plus calcipotriol), monotherapy with vitamin D analogues or vitamin D3 and dithranol are effective.[73] Coal tar and topical retinoids are of limited effect.[74] Regarding safety issues, studies report that vitamin D causes more skin irritation than corticosteroids.[73] Topical corticosteroids carry the risk of skin atrophy and adrenal axis suppression.[75,76]

2.3 Phototherapy

UV radiation improves psoriasis by inducing apoptosis in different cell types of the skin, promoting immunosuppression through the induction of the migration of Langerhans cells out of the epidermis and changing the cytokine profile locally (in the skin) as well as systemically.[77] In the treatment of psoriasis, narrowband UVB therapy has replaced broadband UVB therapy due to its higher efficacy and less side-effects.[78] Although oral 8-methoxyPsoralen-UVA (PUVA) is more efficacious than

narrowband UVB, narrowband UVB is recommended as first choice phototherapy since oral PUVA induces an increased risk of skin cancer and is less easy to use compared with narrowband UVB.[79-81] It is also possible to use home UVB therapy, since this is as effective and safe as narrowband outpatient UVB therapy.[82]

2.4 Conventional systemic therapies

The conventional systemic agents that can be used for psoriasis treatment are methotrexate, fumarates, acitretin and cyclosporine.[67] The long-term use of conventional systemic therapies may be hampered by the development of cumulative end-organ toxicities (methotrexate and cyclosporine) and drug-drug interactions (methotrexate, cyclosporine, acitretin).[2,83]

2.4.1 Methotrexate

Methotrexate is a folic acid antagonist and impairs DNA replication by interfering with the purine synthesis.[67,83] The efficacy of methotrexate is at least similar to that of cyclosporine; 60% reached a PASI75 after 16 weeks of treatment.[67,81,84] Methotrexate can be used for long-term psoriasis treatment.[81] Methotrexate carries the risk of inducing liver fibrosis and cirrhosis, but the quality of studies analyzing this risk is low.[67,83,85] Therefore the question remains whether nonalcoholic fatty liver disease in patients with psoriasis and obesity, dyslipidaemia and diabetes (i.e., metabolic syndrome) is an explanation for the development of methotrexate-induced liver fibrosis.[85] Methotrexate is teratogenic and should not be used by female patients planning their pregnancy as well as male patients that wish to father children.[67,83] Methotrexate should be stopped for at least 3 months before conception in both sexes.[81]

2.4.2 Fumarates

Fumarates exert their effect by inhibiting nuclear factor kappa B and by T-cell apoptosis.[67] Fumarates are well suited for long-term psoriasis therapy. In the Netherlands, fumarates are not registered for the treatment of psoriasis. Physicians should regularly check for lymphocytopenia because severe and longstanding low lymphocytes may lead to the development of progressive multifocal leukoencephalopathy.[81,86,87] Guidelines report a PASI75 of 50-70% at week 16.[81,88]

2.4.3 Acitretin

Acitretin is a retinoid that exert its effect by binding to nuclear retinoid receptors and thereby altering gene transcription. Consequently there is a normalization of the keratinocyte proliferation and differentiation.[67] In the treatment of psoriasis, acitretin monotherapy has a limited efficacy; 23-30% of patients achieve PASI75 after 8-12

weeks.[81,88] It can, however, be used in combination with phototherapy (e.g., Re-UVB, Re-PUVA) or in combination with a biologic. Acitretin monotherapy may be prescribed to treat pustular psoriasis and erythrodermic psoriasis.[67] Retinoids are teratogenic and should only be prescribed with effective contraceptive precautions in women of childbearing age.[67,83]

2.4.4 Cyclosporine

Cyclosporine is an oral calcineurin inhibitor.[67,83] It is an immunosuppressive agent that inhibits the calcineurin phosphatase-initiated activation of T-cells.[67] Cyclosporine has a fast onset of action. Fifty-70% of patients with psoriasis reached a PASI75 after 12-16 weeks of treatment.[81,88] Long-term continuous use of cyclosporine is, however, not recommended due to the development of irreversible renal changes (renal toxicity) in patients with psoriasis.[83]

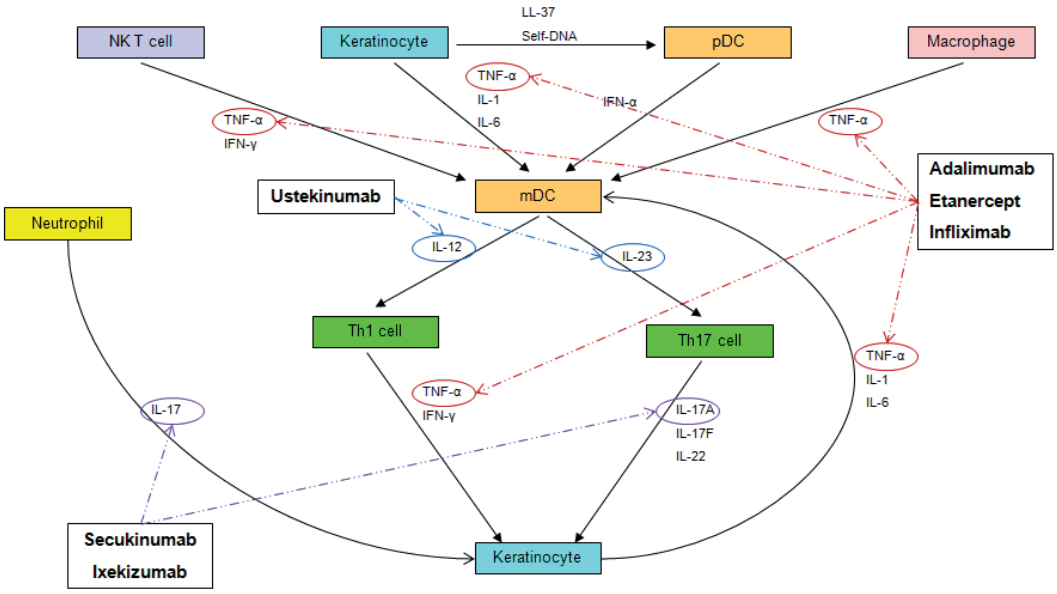
2.5 Biologics

Biologics are proteins produced in living organisms with the use of recombinant DNA technology.[89] They interfere with the immunopathogenesis of psoriasis by, for example, blocking the function of certain proinflammatory cytokines (Figure 2).[90] Biologics currently approved by the European Medicine Agency (EMA) for the treatment of psoriasis are adalimumab, etanercept, infliximab, ustekinumab and more recently secukinumab and ixekizumab. Secukinumab, a fully human anti-IL17A monoclonal antibody, as well as ixekizumab, a humanized anti-IL17A monoclonal antibody, will not be covered in this thesis.[91]

2.5.1 Adalimumab

Adalimumab (Humira®) was approved for the treatment of psoriasis by the EMA in December 2007.[81] Adalimumab is a fully human immunoglobulin G1 (IgG1) monoclonal tumor necrosis factor-alpha (TNF-α) antibody. It binds to TNF-α and blocks its interaction with the TNF receptor and thereby interferes with the immunopathogenesis of psoriasis (Figure 2).[92,93] Adalimumab proteins are produced by recombinant DNA technology in a mammalian cell expression system.[93] Adalimumab is injected subcutaneously by the patient in a dose of 80mg at week 0, 40mg at week 1, followed by 40mg every other week.[81] The efficacy of adalimumab has been assessed in RCTs; 53-80% of patients attained PASI75 at week 16.[81] Adalimumab is suitable for long-term psoriasis treatment.[81,94] Short- and long-term adalimumab treatment appears to be safe.[95-97] The most common adverse events (AEs) reported by patients with psoriasis in RCTs on adalimumab treatment are upper respiratory tract infections, injection site reactions, headache and in some studies muscle pain.[97-102]

Figure 2 Biologics interfere with the immunopathogenesis of psoriasis



Legend:
NK T cell: Natural killer T cell | pDC: plasmacytoid dendritic cell | mDC: myeloid dendritic cell
LL-37: cathelicidin | IFN: interferon | IL: interleukin | TNF: tumor necrosis factor | Th: T helper cell

2.5.2. Etanercept

Etanercept (Enbrel®) was approved by the EMA in September 2004.[81] Etanercept is a fully human dimeric fusion protein.[103-105] It consists of the two FC-regions of human IgG1 and two receptor regions of the human tumor necrosis factor-receptor II (TNF-RII).[103-108] These two receptors are able to bind soluble and membrane-bound TNF-α with an affinity much higher than the naturally occurring monomeric TNF receptors in our body.[106] By binding the proinflammatory cytokine TNF-α, etanercept inhibits the inflammation cascade involved in the development of psoriasis (Figure 2). Etanercept proteins are manufactured in a Chinese hamster ovary expression system using recombinant DNA technology.[103,106] According to label, etanercept is used continuously and is being injected subcutaneously by the patient in a dose of 50mg biweekly during 12 weeks followed by 50mg once weekly or 25mg biweekly.[81] The efficacy of etanercept from RCTs is that in 49% of patients treated with etanercept

50mg biweekly, PASI75 is achieved at 12 weeks of treatment.[81] This response improves until 24 weeks of treatment. Short- and long-term use of etanercept seems to be safe, even when used in different dosing regimens.[109-111] The most common AEs that were mentioned by patients with psoriasis in RCTs on etanercept include upper respiratory tract infections, injection site reactions, headache and in some studies arthralgia and pruritus.[112-120]

2.5.3 Infliximab

Infliximab (Remicade®) was approved by the EMA in September 2005.[81] It is a chimeric (mouse-human) IgG1 monoclonal antibody that binds directly to TNF-α, thereby interfering with the pathogenesis of psoriasis (Figure 2).[104] Infliximab proteins are manufactured in hybridoma cells of mice using recombinant DNA technology.[121,122] Infliximab is administered intravenously in a dose of 5mg/kg at week 0, week 2, week 6 and then every 8 weeks.[81] RCTs on infliximab treatment in patients with psoriasis have shown that PASI75 was reached in approximately 80% of patients at week 10.[81] Infliximab appears to be safe for short- and long-term use, however AEs are common during treatment.[123-126] In a meta-analysis, there was an 18% increased risk of AEs on infliximab treatment compared with placebo treatment across 10-30 weeks of treatment.[126] In that study, the risk of AEs on etanercept was, however, not statistically significantly different compared with placebo for that time period.[126] The most commonly mentioned AEs in RCTs on infliximab include upper respiratory tract infections, headache, increased hepatic enzymes, viral infections and in some studies arthralgia.[123,127-130] Compared with the other biologics, an infliximab-specific AE that might occur is an infusion reaction.[126]

2.5.4 Ustekinumab

Approved by the EMA in January 2009, ustekinumab (Stelara®) is a fully human IgG1 monoclonal antibody that blocks the shared p40 protein subunit of the cytokines IL-12 and IL23.[88,131] It thereby interferes with the immunopathogenesis of psoriasis (Figure 2). Ustekinumab is produced by recombinant DNA technology in transgenic mice.[132] For the treatment of psoriasis, ustekinumab is prescribed in the following doses: 45mg at week 0, week 4 and then every 12 weeks in patients ≤100kg and 90mg at week 0, week 4 and subsequently every 12 weeks in patients >100kg.[88] In RCTs, ustekinumab reaches a PASI75 in 67%-74% of patients treated with 45mg and 68%-71% of patients treated with 90mg at week 12.[88] Ustekinumab seems safe for short- and long-term use.[133-135] Upper respiratory tract infections, headache, arthralgia, cough, injection site reactions, back pain, diarrhea and fatigue were common AEs reported by patients with psoriasis treated with ustekinumab in RCTs.[134-138] Injection site reactions seem to occur more frequently with etanercept than with ustekinumab treatment.[118]

2.6 Small molecules

A more recently approved agent is the small molecule apremilast, an oral phosphodiesterase 4 inhibitor.[139,140] A new and very promising agent is tofacitinib, an oral Janus kinase inhibitor.[141] Small molecules will not be covered in this thesis.

3

Special areas of interest of thesis

This chapter provides background information to the formulated research questions in Chapter 4.

3.1 Effectiveness

Effectiveness is measured in daily practice, while efficacy is measured in RCTs. Antipsoriatic agents have been studied in RCTs and the efficacy of these treatments are summarized in systematic reviews and guidelines. In RCTs, however, a more healthy patient population is included due to strict in- and exclusion criteria. Efficacy and safety results are therefore not automatically generalizable to patients in daily clinical practice.[142,143] To be included in RCTs on biologic agents for psoriasis, patients had to have a moderate to severe psoriasis with a PASI at treatment start of at least 10 or even 12, had to be biologic naïve (i.e., never used a biologic before) or had to be naïve to the (class of) drug investigated. Elderly patients were usually ineligible, as were the patients with multiple comorbidities and comedications, mental illnesses and patients that were expected to show a low adherence to therapy.[97,113,130,138,144] Daily practice differs substantially from RCTs in that patient populations differ, but also the extent to which the patient is affected by psoriasis (in daily practice less severe disease is also treated when a patient has to switch from one biologic agent to another biologic), treatment strategies (dose adjustments, combination therapies), the time a physician is available per patient as well as physician's experiences and preferences with certain agents. In general, the internal validity of RCTs is high and the external validity low, whereas daily practice studies have low internal validity and high external validity.[145] Daily practice studies with patients with psoriasis can therefore be viewed as complementary to RCTs.

3.2 Drug survival

The duration and the probability that patients will stay on a drug over time can be measured with the drug survival. Drug survival is a comprehensive measure of the effectiveness and safety of the drug, but also of certain aspects that are not dependent on the drug itself such as the number of available treatment options, physician's and patient's preferences.[146] Originally, survival indicates the probability that patients are still alive after a certain time period.[147] In the drug survival, it is not the probability that the patient is still alive, but the probability that the patient will still be on the drug. Drug survival is calculated using survival analysis (i.e., Kaplan Meier curves) and it can be split by reasons of discontinuation: ineffectiveness, safety, both reasons or other reasons or whether the patient discontinued the drug in general (all reasons

grouped together). Drug survival can be performed for one drug or for different drugs grouped together.[148] Of note, drug survival is not the same as effectiveness. In drug survival research on psoriasis, for example, when a drug is stopped based on the reason that the drug is not effective (any more), this does not mean that the patient did not reach a PASI75. It only indicates that the physician decided to discontinue the drug because the physician and patient agreed that the drug was not effective enough to treat the psoriasis.

3.3 Improvements of efficacy and effectiveness

3.3.1 Guidelines

Guidelines on the treatment of psoriasis are documents created to provide the physician guidance in treating the patient with psoriasis. Different nations published guidelines on the treatment of psoriasis and these guidelines differ from each other in subtle ways.[81,149-151] Guidelines may have different levels of evidence (State of the art (S)1, S2 or S3). S1-guidelines are based on an informal consensus of an expert group, S2k-guidelines on a structured consensus, S2e-guidelines on a systematic literature assessment and S3-guidelines on systematic reviews and a structured consensus meeting.[152] Until recently, the Dutch S3-guidelines on the treatment of psoriasis had never been published internationally.[153] What the current treatment guidelines on psoriasis have in common is that they contain treatment recommendations for the physician after systematic reviews of the literature. Guidelines on psoriasis provide in this way predominantly evidence on the efficacy and safety of antipsoriatic treatments, usually from RCTs. A difference between the Dutch and German guidelines is that the latter provide physicians with a flow chart on when to switch or adjust treatment in order to improve the effectiveness of agents (treatment goals).[151] As in most guidelines on the treatment of psoriasis data on the commonly used combination therapies with systemic antipsoriatic agents (for example, conventional systemic agents with biologics) are lacking, we summarized this evidence in this thesis.

3.3.2 Treatment goals

In order to help physicians to improve the effectiveness of systemic antipsoriatic treatments and to guide them when to adjust or switch these treatments, PASI50 and PASI75 as well as DLQI have been incorporated into the treatment goals.[64,154,155] When a patient reaches PASI75, treatment may be continued. If a patient does not reach PASI50, treatment should be adjusted. When a patient reaches PASI50 but not PASI75, treatment should be adjusted if DLQI is above 5. With the development of new biologic agents (e.g., secukinumab), PASI90 and even PASI100 are more easily

reached by patients and it is therefore currently debated whether PASI90 should be the new treatment goal instead of PASI75.[156] Recently conducted research which indicates that a correlation seems to exist between the extent of psoriasis (mean percent reduction in PASI) and the quality of life (mean improvement in DLQI) further strengthen the concept of PASI90 as a new treatment goal.[156,157] In a trial on infliximab for psoriasis treatment, patients with a PASI90 had significantly more often a better quality of life score (DLQI of 0-1) when compared with patients with a PASI75 but not achieving a PASI90.[156,158]

3.3.3 Combination therapy

Although combination therapy is common in daily practice psoriasis treatment, guidelines lack data and recommendations on this treatment option. Combination of treatments might be necessary in order to treat psoriasis and its comorbidity psoriatic arthritis, but a second agent could also be started in order to achieve higher efficacy/ effectiveness, or to be able to lower the dose of the first agent, or to attack the antibodies the patient has formed during the first agent.[159] This thesis will provide the reader with evidence from RCTs that have been performed on combination therapy with systemic agents in psoriasis treatment.

4

Aims of thesis and research questions

4.1 Aims of thesis

The major aims of this thesis are (1) to explore, compare and predict the effectiveness of biologics for psoriasis in daily practice and (2) to explore, compare and predict treatment success of biologics for psoriasis with drug survival and (3) to explore those areas with room for improvement in daily practice psoriasis care.

4.2 Research questions

4.2.1 Effectiveness

To explore

1: What is known thus far from literature on the effectiveness of biologics in daily practice psoriasis treatment?

To compare

2: Which biologic has the highest confounder-corrected effectiveness in daily practice psoriasis treatment using data from our prospective BioCAPTURE cohort?

To predict

3: What are predictors for high clinical effectiveness of biologics for psoriasis in daily clinical practice using data from BioCAPTURE?

4.2.2 Drug survival

To explore

4: What is the long-term overall drug survival of adalimumab, etanercept, and ustekinumab in patients with psoriasis?

5: Is drug survival accompanied with a good skin-specific quality of life in patients with psoriasis?

To compare

6: Which biologic has the highest confounder-corrected, long-term, overall drug survival in patients with psoriasis?

7: Which biologic has the highest confounder-corrected, long-term drug survival split for reasons of discontinuation, i.e. ineffectiveness and side-effects, in patients with psoriasis?

To predict

8: What are the predictors of long-term overall drug survival of biologics in patients with psoriasis?

9: What are the predictors of long-term drug survival split for biologics and split for reasons of discontinuation, i.e. ineffectiveness and side-effects, in patients with psoriasis?

4.2.3 Improvements of efficacy and effectiveness

To explore

10: What are the guidelines that dermatologists in the Netherlands should adhere to when treating patients with psoriasis in daily practice?

11: Since information on systemic combination therapy is largely lacking in current guidelines on psoriasis treatment, what is the current evidence from RCTs on systemic combination treatment in psoriasis?

12: Do dermatologists already intuitively apply 'treatment goals' in patients with psoriasis treated with biologics in daily practice?

References

1 Schon MP, Boehncke WH. Psoriasis. The New England journal of medicine 2005; 352: 1899-912.
2 Boehncke WH, Schon MP. Psoriasis. Lancet 2015; 386: 983-94.
3 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007; 370: 263-71.
4 Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. JAMA dermatology 2015; 151: 651-8.
5 Armstrong AW, Schupp C, Wu J et al. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. PloS one 2012; 7: e52935.
6 Rapp SR, Feldman SR, Exum ML et al. Psoriasis causes as much disability as other major medical diseases. Journal of the American Academy of Dermatology 1999; 41: 401-7.
7 Nestle FO, Kaplan DH, Barker J. Psoriasis. The New England journal of medicine 2009; 361: 496-509.
8 Glickman FS. Lepra, psora, psoriasis. Journal of the American Academy of Dermatology 1986; 14: 863-6.
9 Hrehorow E, Salomon J, Matusiak L et al. Patients with psoriasis feel stigmatized. Acta dermato-venereologica 2012; 92: 67-72.
10 Guenther L, Han C, Szapary P et al. Impact of ustekinumab on health-related quality of life and sexual difficulties associated with psoriasis: results from two phase III clinical trials. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25: 851-7.
11 Halioua B, Sid-Mohand D, Roussel ME et al. Extent of misconceptions, negative prejudices and discriminatory behaviour to psoriasis patients in France. Journal of the European Academy of Dermatology and Venereology : JEADV 2016; 30: 650-4.
12 Holubar K. Psoriasis and parapsoriasis: since 200 and 100 years, respectively. Journal of the European Academy of Dermatology and Venereology : JEADV 2003; 17: 126-7.
13 Grzybowski A, Nita M. Leprosy in the Bible. Clinics in dermatology 2016; 34: 3-7.
14 Meenan FO. A note on the history of psoriasis. Irish journal of medical science 1955: 141-2.
15 Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. The Journal of clinical investigation 2004; 113: 1664-75.
16 Ingram JT. The significance and management of psoriasis. British medical journal 1954; 2: 823-8.
17 Farber EM, McClintock RP, Jr. A current review of psoriasis. California medicine 1968; 108: 440-57.
18 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. Journal of the American Academy of Dermatology 2014; 70: 512-6.
19 Alexis AF, Blackcloud P. Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances. The Journal of clinical and aesthetic dermatology 2014; 7: 16-24.
20 Kubota K, Kamijima Y, Sato T et al. Epidemiology of psoriasis and palmoplantar pustulosis: a nationwide study using the Japanese national claims database. BMJ open 2015; 5: e006450.
21 Parisi R, Symmons DP, Griffiths CE et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. The Journal of investigative dermatology 2013; 133: 377-85.
22 Hagg D, Eriksson M, Sundstrom A et al. The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. PloS one 2013; 8: e63619.
23 Gunawardena DA, Gunawardena KA, Vasanthanathan NS et al. Psoriasis in Sri-Lanka--a computer analysis of 1366 cases. The British journal of dermatology 1978; 98: 85-96.
24 Gelfand JM, Weinstein R, Porter SB et al. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Archives of dermatology 2005; 141: 1537-41.
25 Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. Journal of the American Academy of Dermatology 1985; 13: 450-6.
26 Naldi L, Gambini D. The clinical spectrum of psoriasis. Clinics in dermatology 2007; 25: 510-8.
27 Buxton PK. ABC of Dermatology. Psoriasis. Br Med J (Clin Res Ed) 1987; 295: 904-6.
28 Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. Dermatologica 1974; 148: 1-18.
29 de Jong EM. The course of psoriasis. Clinics in dermatology 1997; 15: 687-92.
30 Hebert HL, Ali FR, Bowes J et al. Genetic susceptibility to psoriasis and psoriatic arthritis: implications for therapy. The British journal of dermatology 2012; 166: 474-82.

31 Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. Bmj 2007; 334: 1218-20.
32 Tauscher AE, Fleischer AB, Jr., Phelps KC et al. Psoriasis and pregnancy. Journal of cutaneous medicine and surgery 2002; 6: 561-70.
33 Gudjonsson JE, Elder JT. Psoriasis: epidemiology. Clinics in dermatology 2007; 25: 535-46.
34 Armstrong AW, Armstrong EJ, Fuller EN et al. Smoking and pathogenesis of psoriasis: a review of oxidative, inflammatory and genetic mechanisms. The British journal of dermatology 2011; 165: 1162-8.
35 Armstrong AW. Psoriasis provoked or exacerbated by medications: identifying culprit drugs. JAMA dermatology 2014; 150: 963.
36 Brenaut E, Horreau C, Pouplard C et al. Alcohol consumption and psoriasis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology : JEADV 2013; 27 Suppl 3: 30-5.
37 Jensen P, Zachariae C, Christensen R et al. Effect of weight loss on the cardiovascular risk profile of obese patients with psoriasis. Acta dermato-venereologica 2014; 94: 691-4.
38 Gaspari AA. Innate and adaptive immunity and the pathophysiology of psoriasis. Journal of the American Academy of Dermatology 2006; 54: S67-80.
39 Gupta R, Debbaneh MG, Liao W. Genetic Epidemiology of Psoriasis. Current dermatology reports 2014; 3: 61-78.
40 Tonel G, Conrad C. Interplay between keratinocytes and immune cells--recent insights into psoriasis pathogenesis. The international journal of biochemistry & cell biology 2009; 41: 963-8.
41 Johnson-Huang LM, McNutt NS, Krueger JG et al. Cytokine-producing dendritic cells in the pathogenesis of inflammatory skin diseases. Journal of clinical immunology 2009; 29: 247-56.
42 Keijsers RR, Joosten I, van Erp PE et al. Cellular sources of IL-17 in psoriasis: a paradigm shift? Experimental dermatology 2014; 23: 799-803.
43 Oka A, Mabuchi T, Ozawa A et al. Current understanding of human genetics and genetic analysis of psoriasis. The Journal of dermatology 2012; 39: 231-41.
44 Farber EM, Nall ML, Watson W. Natural history of psoriasis in 61 twin pairs. Archives of dermatology 1974; 109: 207-11.
45 Chandra A, Ray A, Senapati S et al. Genetic and epigenetic basis of psoriasis pathogenesis. Molecular immunology 2015; 64: 313-23.
46 Eder L, Chandran V, Gladman DD. What have we learned about genetic susceptibility in psoriasis and psoriatic arthritis? Current opinion in rheumatology 2015; 27: 91-8.
47 de Cid R, Riveira-Munoz E, Zeeuwen PL et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nature genetics 2009; 41: 211-5.
48 Willemsen R, Roseeuw D, Vanderlinden J. Alexithymia and dermatology: the state of the art. International journal of dermatology 2008; 47: 903-10.
49 Gupta MA, Simpson FC, Gupta AK. Psoriasis and sleep disorders: A systematic review. Sleep medicine reviews 2015; 29: 63-75.
50 van de Kerkhof PC. Increased prevalence of psoriasis in patients with coronary artery disease. The British journal of dermatology 2014; 171: 450.
51 Ni C, Chiu MW. Psoriasis and comorbidities: links and risks. Clinical, cosmetic and investigational dermatology 2014; 7: 119-32.
52 Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. Journal of the National Cancer Institute 1998; 90: 1278-84.
53 van Lumig PP, Menting SP, van den Reek JM et al. An increased risk of non-melanoma skin cancer during TNF-inhibitor treatment in psoriasis patients compared to rheumatoid arthritis patients probably relates to disease-related factors. Journal of the European Academy of Dermatology and Venereology : JEADV 2015; 29: 752-60.
54 Stern RS, Nijsten T, Feldman SR et al. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. The journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research 2004; 9: 136-9.

55 Finlay AY, Basra MK, Piguet V et al. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. The Journal of investigative dermatology 2012; 132: 2464-5.
56 Bronsard V, Paul C, Prey S et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. Journal of the European Academy of Dermatology and Venereology : JEADV 2010; 24 Suppl 2: 17-22.
57 Hongbo Y, Thomas CL, Harrison MA et al. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? The Journal of investigative dermatology 2005; 125: 659-64.
58 Martinez-Garcia E, Arias-Santiago S, Valenzuela-Salas I et al. Quality of life in persons living with psoriasis patients. Journal of the American Academy of Dermatology 2014; 71: 302-7.
59 Spuls PI, Lecluse LL, Poulsen ML et al. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. The Journal of investigative dermatology 2010; 130: 933-43.
60 Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology 2012; 66: 369-75.
61 Puzenat E, Bronsard V, Prey S et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. Journal of the European Academy of Dermatology and Venereology : JEADV 2010; 24 Suppl 2: 10-6.
62 de Rie MA, Goedkoop AY, Bos JD. Overview of psoriasis. Dermatologic therapy 2004; 17: 341-9.
63 Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica 1978; 157: 238-44.
64 Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Archives of dermatological research 2011; 303: 1-10.
65 Finlay AY. Current severe psoriasis and the rule of tens. The British journal of dermatology 2005; 152: 861-7.
66 Nast A, Jacobs A, Rosumeck S et al. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. The Journal of investigative dermatology 2015; 135: 2641-8.
67 Menter A, Griffiths CE. Current and future management of psoriasis. Lancet 2007; 370: 272-84.
68 Tan KW, Griffiths CE. Novel systemic therapies for the treatment of psoriasis. Expert opinion on pharmacotherapy 2016; 17: 79-92.
69 Koetsier MI, van de Kerkhof PC. "Patient-centered treatment" for mild-to-moderate psoriasis. The Journal of dermatological treatment 2015; 26: 1-6.
70 van de Kerkhof PC. How to personalize the treatment of psoriasis with biologics? The Journal of dermatological treatment 2015; 26: 101-2.
71 Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007; 445: 866-73.
72 Thorneloe RJ, Bundy C, Griffiths CE et al. Adherence to medication in patients with psoriasis: a systematic literature review. The British journal of dermatology 2013; 168: 20-31.
73 Mason A, Mason J, Cork M et al. Topical treatments for chronic plaque psoriasis: an abridged Cochrane systematic review. Journal of the American Academy of Dermatology 2013; 69: 799-807.
74 Samarasekera EJ, Sawyer L, Wonderling D et al. Topical therapies for the treatment of plaque psoriasis: systematic review and network meta-analyses. The British journal of dermatology 2013; 168: 954-67.
75 Castela E, Archier E, Devaux S et al. Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 3: 47-51.
76 Horn EJ, Domm S, Katz HI et al. Topical corticosteroids in psoriasis: strategies for improving safety. Journal of the European Academy of Dermatology and Venereology : JEADV 2010; 24: 119-24.
77 Wong T, Hsu L, Liao W. Phototherapy in psoriasis: a review of mechanisms of action. Journal of cutaneous medicine and surgery 2013; 17: 6-12.
78 Honigsmann H. Phototherapy for psoriasis. Clinical and experimental dermatology 2001; 26: 343-50.
79 Archier E, Devaux S, Castela E et al. Efficacy of psoralen UV-A therapy vs. narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 3: 11-21.

80 Archier E, Devaux S, Castela E et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 3: 22-31.
81 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV 2009; 23 Suppl 2: 1-70.
82 Koek MB, Buskens E, van Weelden H et al. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). Bmj 2009; 338: b1542.
83 Hsu S, Papp KA, Lebwohl MG et al. Consensus guidelines for the management of plaque psoriasis. Archives of dermatology 2012; 148: 95-102.
84 Heydendael VM, Spuls PI, Opmeer BC et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. The New England journal of medicine 2003; 349: 658-65.
85 Maybury CM, Jabbar-Lopez ZK, Wong T et al. Methotrexate and liver fibrosis in people with psoriasis: a systematic review of observational studies. The British journal of dermatology 2014; 171: 17-29.
86 Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. The New England journal of medicine 2015; 372: 1476-8.
87 Nieuwkamp DJ, Murk JL, van Oosten BW et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. The New England journal of medicine 2015; 372: 1474-6.
88 Nast A, Boehncke WH, Mrowietz U et al. German S3-guidelines on the treatment of psoriasis vulgaris (short version). Archives of dermatological research 2012; 304: 87-113.
89 Mehlis SL, Gordon KB. The immunology of psoriasis and biologic immunotherapy. Journal of the American Academy of Dermatology 2003; 49: S44-50.
90 Walsh SR, Shear NH. Psoriasis and the new biologic agents: interrupting a T-AP dance. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2004; 170: 1933-41.
91 Langley RG, Elewski BE, Lebwohl M et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. The New England journal of medicine 2014; 371: 326-38.
92 Bain B, Brazil M. Adalimumab. Nature reviews. Drug discovery 2003; 2: 693-94.
93 Scheinfeld N. Adalimumab (Humira): a brief review for dermatologists. The Journal of dermatological treatment 2004; 15: 348-52.
94 Gordon K, Papp K, Poulin Y et al. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. Journal of the American Academy of Dermatology 2012; 66: 241-51.
95 Burmester GR, Panaccione R, Gordon KB et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Annals of the rheumatic diseases 2013; 72: 517-24.
96 Leonardi C, Papp K, Strober B et al. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. American journal of clinical dermatology 2011; 12: 321-37.
97 Gordon KB, Langley RG, Leonardi C et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. Journal of the American Academy of Dermatology 2006; 55: 598-606.
98 Menter A, Tyring SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. Journal of the American Academy of Dermatology 2008; 58: 106-15.
99 Saurat JH, Stingl G, Dubertret L et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). The British journal of dermatology 2008; 158: 558-66.
100 Menter A, Gordon KB, Leonardi CL et al. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. Journal of the American Academy of Dermatology 2010; 63: 448-56.
101 Thaci D, Ortonne JP, Chimenti S et al. A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study. The British journal of dermatology 2010; 163: 402-11.

102 Ortonne JP, Chimenti S, Reich K et al. Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25: 1012-20.
103 Goffe B, Cather JC. Etanercept: An overview. Journal of the American Academy of Dermatology 2003; 49: S105-11.
104 Weinberg JM. An overview of infliximab, etanercept, efalizumab, and alefacept as biologic therapy for psoriasis. Clinical therapeutics 2003; 25: 2487-505.
105 Weinberg JM, Saini R. Biologic therapy for psoriasis: the tumor necrosis factor inhibitors infliximab and etanercept. Cutis 2003; 71: 25-9.
106 Papp KA. Etanercept in psoriasis. Expert opinion on pharmacotherapy 2004; 5: 2139-46.
107 Gottlieb AB. Etanercept for the treatment of psoriasis and psoriatic arthritis. Dermatologic therapy 2004; 17: 401-8.
108 Tan JK, Aphale A, Malaviya R et al. Mechanisms of action of etanercept in psoriasis. The journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research 2007; 12: 38-45.
109 Kimball AB, Rothman KJ, Kricorian G et al. OBSERVE-5: observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results. Journal of the American Academy of Dermatology 2015; 72: 115-22.
110 Pariser DM, Leonardi CL, Gordon K et al. Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. Journal of the American Academy of Dermatology 2012; 67: 245-56.
111 Kivelevitch D, Mansouri B, Menter A. Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. Biologics : targets & therapy 2014; 8: 169-82.
112 Gottlieb AB, Matheson RT, Lowe N et al. A randomized trial of etanercept as monotherapy for psoriasis. Archives of dermatology 2003; 139: 1627-32; discussion 32.
113 Leonardi CL, Powers JL, Matheson RT et al. Etanercept as monotherapy in patients with psoriasis. The New England journal of medicine 2003; 349: 2014-22.
114 Papp KA, Tyring S, Lahfa M et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. The British journal of dermatology 2005; 152: 1304-12.
115 Tyring S, Gottlieb A, Papp K et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006; 367: 29-35.
116 Moore A, Gordon KB, Kang S et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. Journal of the American Academy of Dermatology 2007; 56: 598-603.
117 van de Kerkhof PC, Segaert S, Lahfa M et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. The British journal of dermatology 2008; 159: 1177-85.
118 Griffiths CE, Strober BE, van de Kerkhof P et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. The New England journal of medicine 2010; 362: 118-28.
119 Gottlieb AB, Langley RG, Strober BE et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. The British journal of dermatology 2012; 167: 649-57.
120 Lebwohl MG, Kircik L, Callis Duffin K et al. A randomized study to evaluate the efficacy and safety of adding topical therapy to etanercept in patients with moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology 2013; 69: 385-92.
121 Gottlieb AB. Infliximab for psoriasis. Journal of the American Academy of Dermatology 2003; 49: S112-7.
122 Valle E, Gross M, Bickston SJ. Infliximab. Expert opinion on pharmacotherapy 2001; 2: 1015-25.
123 Chaudhari U, Romano P, Mulcahy LD et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001; 357: 1842-7.
124 Shear NH, Hartmann M, Toledo-Bahena M et al. Long-term efficacy and safety of infliximab maintenance therapy in patients with plaque-type psoriasis in real-world practice. The British journal of dermatology 2014; 171: 631-41.

125 Torii H, Terui T, Matsukawa M et al. Safety profiles and efficacy of infliximab therapy in Japanese patients with plaque psoriasis with or without psoriatic arthritis, pustular psoriasis or psoriatic erythroderma: Results from the prospective post-marketing surveillance. The Journal of dermatology 2015.
126 Brimhall AK, King LN, Licciardone JC et al. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. The British journal of dermatology 2008; 159: 274-85.
127 Barker J, Hoffmann M, Wozel G et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). The British journal of dermatology 2011; 165: 1109-17.
128 Reich K, Wozel G, Zheng H et al. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). The British journal of dermatology 2013; 168: 1325-34.
129 Torii H, Nakagawa H, Japanese Infliximab Study i. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. Journal of dermatological science 2010; 59: 40-9.
130 Reich K, Nestle FO, Papp K et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005; 366: 1367-74.
131 Cingoz O. Ustekinumab. mAbs 2009; 1: 216-21.
132 Benson JM, Peritt D, Scallon BJ et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. mAbs 2011; 3: 535-45.
133 Kumar N, Narang K, Cressey BD et al. Long-term safety of ustekinumab for psoriasis. Expert opinion on drug safety 2013; 12: 757-65.
134 Lebwohl M, Leonardi C, Griffiths CE et al. Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis (Part I of II): results from analyses of general safety parameters from pooled Phase 2 and 3 clinical trials. Journal of the American Academy of Dermatology 2012; 66: 731-41.
135 Papp KA, Griffiths CE, Gordon K et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. The British journal of dermatology 2013; 168: 844-54.
136 Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1665-74.
137 Kimball AB, Gordon KB, Fakharzadeh S et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. The British journal of dermatology 2012; 166: 861-72.
138 Papp KA, Langley RG, Lebwohl M et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008; 371: 1675-84.
139 Papp K, Reich K, Leonardi CL et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Journal of the American Academy of Dermatology 2015; 73: 37-49.
140 Paul C, Cather J, Gooderham M et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). The British journal of dermatology 2015; 173: 1387-99.
141 Papp KA, Krueger JG, Feldman SR et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. Journal of the American Academy of Dermatology 2016.
142 Kievit W, Fransen J, Oerlemans AJ et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Annals of the rheumatic diseases 2007; 66: 1473-8.

143 Garcia-Doval I, Carretero G, Vanaclocha F et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Archives of dermatology 2012; 148: 463-70.
144 Nijsten T, Wakkee M. Psocare: Italy shows the way in postmarketing studies. Dermatology 2008; 217: 362-4.
145 Kennedy-Martin T, Curtis S, Faries D et al. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015; 16: 495.
146 van den Reek JM, Kievit W, Gniadecki R et al. Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls. The Journal of investigative dermatology 2015; 135: e34.
147 Steiner PE, Maimon SN, et al. Gastric cancer; morphologic factors in 5-year survival after gastrectomy. The American journal of pathology 1948; 24: 947-69.
148 Warren RB, Smith CH, Yiu ZZ et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). The Journal of investigative dermatology 2015; 135: 2632-40.
149 Smith CH, Anstey AV, Barker JN et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. The British journal of dermatology 2009; 161: 987-1019.
150 Menter A, Gottlieb A, Feldman SR et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Journal of the American Academy of Dermatology 2008; 58: 826-50.
151 Nast A, Boehncke WH, Mrowietz U et al. [S3-guidelines for the treatment of psoriasis vulgaris Update 2011]. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 2011; 9 Suppl 2: S1-104.
152 Werner RN, Marinovic B, Rosumeck S et al. The quality of European dermatological guidelines: critical appraisal of the quality of EDF guidelines using the AGREE II instrument. Journal of the European Academy of Dermatology and Venereology : JEADV 2016; 30: 395-403.
153 Spuls PI, Tuut MK, van Everdingen JJ et al. [The practice guideline 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis']. Nederlands tijdschrift voor geneeskunde 2004; 148: 2121-5.
154 Mrowietz U, Kragballe K, Nast A et al. Strategies for improving the quality of care in psoriasis with the use of treatment goals--a report on an implementation meeting. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25 Suppl 3: 1-13.
155 Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 2: 12-20.
156 Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2015; 29: 645-8.
157 Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 333-7.
158 Torii H, Sato N, Yoshinari T et al. Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: an analysis of Japanese clinical trials of infliximab. The Journal of dermatology 2012; 39: 253-9.
159 Jensen P, Skov L, Zachariae C. Systemic combination treatment for psoriasis: a review. Acta dermato-venereologica 2010; 90: 341-9.

PART II

EFFECTIVENESS

5

Effectiveness of biologic and conventional systemic therapies in adults with chronic plaque type psoriasis in daily practice: a systematic review

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Abstract

The efficacy of biologic or conventional systemic therapies for psoriasis has been shown in randomized controlled trials. Effectiveness, however, has been studied in daily practice cohorts, and no aggregation of effectiveness data is available. This systematic review searched PubMed and EMBASE and summarized the real-world evidence on effectiveness of biologics (adalimumab, etanercept, infliximab and ustekinumab) and conventional systemic therapies (acitretin, cyclosporine, fumarates and methotrexate) for the treatment of plaque psoriasis in adults. Thirty-two studies were included. Few data were available on infliximab, ustekinumab and conventional systemics. Results show that biologics and conventional systemics were effective in real-life treatment of psoriasis, with large ranges in the percentage of patients reaching 75% improvement in psoriasis area and severity index score compared with baseline, especially for etanercept and adalimumab treatment. Combination therapies of biologics with conventional systemics, and dose adjustments of biologics were frequently applied strategies and may explain the large range in improvements between cohorts.

Introduction

Psoriasis is a common chronic skin disease, with a prevalence of 2–4% (1). Different therapeutics have been developed to treat this burdensome disease (2–4). Randomized controlled clinical trials (RCTs) have analysed the efficacy of biologic agents (adalimumab, etanercept, infliximab and ustekinumab) and conventional systemic therapies (acitretin, cyclosporine, fumarates and methotrexate) (5–7). Effectiveness data from real-life, observational studies, however, are of added value, since patients and treatment strategies in daily practice differ substantially from those in RCTs (8). The aim of this study was to systematically search the literature to provide an overview of the current evidence on the effectiveness in daily practice of biologic and conventional systemic therapies for the treatment of adults with plaque psoriasis. Short-term (week 12–16), intermediate-term (> 16–≤ 28 weeks) and long-term (≥ 1 year) Psoriasis Area and Severity Index (PASI) responses were investigated. The primary objective was to show the proportion of patients that reached PASI75 (a 75% reduction in PASI score) with biologic and/or conventional systemic agents at week 12–16.

Materials and methods

A systematic literature search was performed on the effectiveness of treatment with biologics or conventional systemics in patients with plaque psoriasis in daily practice. Inclusion and exclusion criteria are described in Table SI. The decision was arbitrarily made to exclude studies in which the number of patients included at baseline was < 30, since in these articles the influence of every additional patient reaching PASI75 has a large influence on the total percentage.

Outcomes

The following outcome measures were chosen (9): (i) PASI (10); (ii) Physician's Global Assessment (PhGA) on a scale of 0–5, 0–6 or 0–7 (11); and (iii) body surface area (BSA) (11).

Primary outcome. The primary outcome was the PASI75 score for biologic and conventional systemic agents in daily clinical practice at week 12–16.

Secondary outcomes. Secondary outcome measures were PASI75 with intermediate-term (17–28 weeks) and long-term (≥ 1 year data) treatment, as well as PASI50, PASI90, PASI100 and decrease in mean PASI, PhGA and BSA with short-, intermediate- and long-term treatment.

All measures were compared with baseline except if stated otherwise.

Search strategy

Two electronic databases (Pubmed and EMBASE) were systematically searched, and studies from 1990 until May 2014 were included. The term "psoriasis" was combined with terms for study design, treatments of interest and outcome measures for effectiveness (Table SII).

Data extraction

Two authors (JZ and MEO) independently screened titles and abstracts, and checked full articles for inclusion and exclusion criteria as well as references for other eligible studies. Data were extracted from text, tables or as numbers in figures and are shown in Table SIII. Any differences in decisions about inclusion or extraction were resolved by consensus or discussion with a third author (EdJ). The results for PASI75 were divided into cohorts using monotherapy and cohorts combining biologic with conventional systemic treatments in some or all of the patients during the study period, prospective vs. retrospective and short-, intermediate- and long-term results of treatment. PASI75 from per protocol analyses are shown. Comparative studies are described in a separate section.

Results

A total of 32 articles were included (Fig. 1): 28 on biologics, 3 on conventional systemic therapies, and 1 describing both biologic and conventional systemic treatment (Table SIII). Seven articles reported results of adalimumab therapy, 20 of etanercept, 4 of infliximab, 4 of ustekinumab, 1 of acitretin, 2 of fumarates, 1 of cyclosporine and 3 of methotrexate. There were 12 prospective and 20 retrospective studies. Results from comparative studies and dosing of biologics are described below in separate sections. For all effectiveness results the reader is referred to Table SIII.

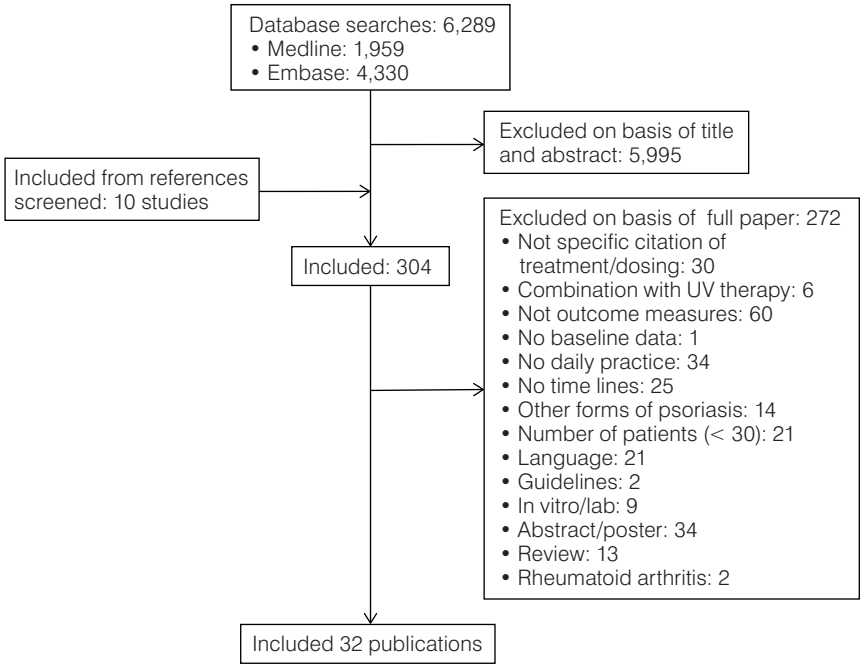
Biologic therapies

Twenty-eight articles (12–39) reported data on biologic therapies and one article (40) compared biologic and conventional systemic treatment. For adalimumab the mean baseline PASI scores of patient cohorts ranged from 10.9 to 20.1, for etanercept these ranges were 11.3–25.6, for infliximab 14.7–17.7, and for ustekinumab 9.6–22.9.

Adalimumab

Study characteristics. Of the 7 articles studying the effectiveness of adalimumab, 3 were prospective (13, 17, 18) and 4 retrospective studies (12, 14–16), including a total of 461 patients. In the study of Van Lümig et al. (13), only those patients whose treatment with etanercept had failed and who had switched to adalimumab were

Figure 1 In- and excluded studies



included, and thus they represented a highly selected patient group. The results from this study were therefore not included for data aggregation. Dosing regimens varied amongst studies, as well as naïvety for biologics, and the number of patients using adalimumab in combination with a conventional systemic agent. One retrospective study (12) reported the results of adalimumab monotherapy. All 7 studies (12–18) reported on long-term therapy results. In all 7 studies (12–18) conventional systemic agents were allowed, but no specification was made of the duration and dosages used. Combination with a conventional systemic was used in 7–41% (12–18) of patients. Methotrexate was used most often. In all studies, the induction dose was per license (80 mg at the start and 40 mg at week 1). The maintenance dose was 40 mg every other week for most patients. However, in all studies dose adjustments were allowed. A dose increase to 40 mg weekly or 40 mg every 10 days was made in 2–36% (12, 14–16, 18) of patients. In 2 studies, the mean weekly dose of adalimumab was 23 mg (13) and 24 mg (17), respectively. In 2 studies (17, 18), a total of 46 patients were treated with 40 mg per 3–4 weeks. The mean duration of dose increases/decreases were not mentioned.

PASI75 outcome for adalimumab. Overall, PASI75 was attained by 27–68% with short-term, 31–82% with intermediate-term and 44–89% with long-term (1 and 2 year) adalimumab treatment (Table SIII).
Adalimumab monotherapy. In the one retrospective study (12), adalimumab reached PASI75 percentages of 38% at week 16, 62% at week 24 and 69% at one year.
Cohorts using adalimumab with conventional systemic treatments. PASI75 results from prospective studies were 27–54% (17, 18) at week 12, 31% (17) at week 24, and 44% (17) at 2 years of adalimumab treatment. In retrospective studies, 56–68% (12, 14–16) of patients reached PASI75 at week 16 (of which only one study (14) used licensed dosing), 50–82% (12, 14–16) at week 24, 48–89% (12, 14–16) at 1 year and 83% (16) at 2 years.

Etanercept
Study characteristics. Twenty articles studied etanercept therapy in daily clinical practice (Table SIII). Nine studies (13, 18, 20, 22, 24, 26, 32, 33, 35) were prospective and 11 retrospective (19, 21, 23, 25, 27–31, 34, 40), including a total of 2,079 patients. Five of 20 articles (21, 25, 29, 31, 40) reported results on etanercept monotherapy. In 7 studies (13, 21, 25, 27, 30, 33, 40) all patients were naïve for biologics, in 12 articles a proportion of patients was non-naïve for biologic therapy. In one article (28) a highly selected group of patients was treated with etanercept, since all patients switched from efalizumab therapy. Results from this study were not included for data aggregation, but can be found in Table SIII. Dosing regimens varied amongst studies. It was explored whether PASI75 results differed between cohorts using either 50 mg biweekly or 25 mg biweekly as induction dose, but no direct comparisons were found. PASI75 percentage ranges were similar, and thus an aggregation of all PASI75 percentages is presented here.
Ten studies (13, 18, 23, 25, 29–33, 35) reported long- term results. No prospective studies reported solely on etanercept monotherapy. In 15 studies it was reported whether a combination therapy with a conventional systemic agent was prescribed and the percentages ranged from 0% to 69% (13, 18–20, 22, 24, 27, 28, 30–35, 40).
When combination therapy was allowed, methotrexate was used most often. Eight articles studied the licensed dosing of etanercept in (part of) the study and 12 studies (13, 18, 19, 22–25, 27, 29, 32, 33, 35) mentioned the ability for physicians to adjust the dose, but did not always provide a detailed description. Nine to 26% (18, 23, 27, 29, 33) of patients had their dose adjusted to 50 mg biweekly during maintenance treatment and 3 studies reported a mean weekly dose of etanercept: 64.1 mg (35), 68.3 mg (32) and 73.4 mg (13).
PASI75 outcome for etanercept. Overall, PASI75 was attained by 12–66% with short-term, 19–85% with intermediate-term, and 49–92.3% with long-term (1- and 2-year) etanercept treatment.

Etanercept monotherapy. Retrospective studies reported a PASI75 of 36.1–54.1 (21, 31) at week 12, 66% (25) at week 16 and 60.5–85% (21, 25, 29, 31) at week 24. At 1 year PASI75 was 71.4–92.3% (25, 29, 31) and at 2 years 86.9% (31).
Cohorts using etanercept with conventional systemic treatments. In prospective studies, etanercept achieved a PASI75 in 12–63% (13, 18, 22, 26, 32, 33) at week 12 and 19–73.2% (13, 24, 26, 32, 33, 35) at week 24 and 25–69.2% (13, 32, 33, 35) at 1 year. In retrospective studies 21.4–26% (19, 27, 30, 34) of patients achieved PASI75 at week 12, 37–53% (23, 27, 30, 34) at week 24, and 49–54% (23, 30) at one year.
Dosing of etanercept. Of the 8 articles studying the licensed dosing of etanercept in (part of) the study, 20–43% and 50–73.2% of patients achieved PASI75 at short- and intermediate-term, respectively (Table SIII).

Infliximab

Study characteristics. Four articles were included, 2 prospective (18, 36) and 2 retrospective studies (40, 41), including a total of 215 patients starting on infliximab. Two of 4 articles (36, 40) reported on infliximab monotherapy. Except for one study (18), all studies prescribed the licensed dose of infliximab. No study mentioned long-term results for PASI75. Combination therapy with a conventional systemic was prescribed in 5% (18) and 81% (41) of patients. Methotrexate was used most often. In 2 studies (18, 41) physicians decreased the dose interval (=dose increase) of infliximab in 10–23% of patients.
PASI75 outcome for infliximab. Overall, PASI75 was attained by 38–53% at short-term and 69% at intermediate-term treatment with infliximab.
Infliximab monotherapy. There were no PASI75 results from studies at week 12, 24 or on long-term treatment with infliximab monotherapy. At week 28, PASI75 was 69% (36) in one prospective study.
Cohorts using infliximab with conventional systemic treatments. In the prospective study with combination therapy and dose adjustment (18), 38% of the patients who previously used biologics and 53% of biologic naïve patients reached PASI75 at week 12.

Ustekinumab

Study characteristics. Four articles described results for ustekinumab; 2 prospective (36, 37) and 2 retrospective studies (38, 39), including a total of 315 patients starting on ustekinumab. Both prospective studies (36, 37) reported on ustekinumab monotherapy. In all but one article (39) a licensed dose of ustekinumab was prescribed. One retrospective study (38) showed long-term results. Combination therapy with a conventional systemic was prescribed in 9–14% (38, 39) of patients and methotrexate was used most often. In one study (39) the dose interval of ustekinumab was adjusted (dose increase) in 8% of treated patients due to a partial relapse several weeks prior to the next injection.

PASI75 outcome for ustekinumab. Overall, PASI75 was attained by 63–80% at short-term, 58–75.9% at intermediate-term, and 65.5% at long-term (1 year data) with ustekinumab treatment.
Ustekinumab monotherapy. Prospectively, PASI75 was attained by 80% (37) of patients at week 16 and 58% (36) at week 28 with ustekinumab monotherapy.
Cohorts using ustekinumab with conventional systemic therapy. Two retrospective studies, of which one (39) was with dose adjustments, were included and presented a PASI75 of 79.3% (39) at week 12 and 63% (38) at week 16, 66.7–75.9% (38, 39) at week 24, and 65.5% (39) at 1 year.

Naïve vs. non-naïve patients treated with biologics

Only a minority of included articles tried to assess the difference in biologic response between naïve and non- naïve patients, but in most of these articles baseline PASI score between both groups was not compared. In only 3 articles (2 adalimumab and 1 ustekinumab) (16, 17, 39) it was stated that baseline PASI score was comparable between groups. For adalimumab, biologic naïve patients seemed to respond better compared with non-naïve patients, as measured with PASI75 at certain time-points and for ustekinumab the same phenomenon was found for anti-tumour necrosis factor alpha (TNF-α) naïve and non-naïve patients.

Conventional systemic therapies

Four articles (40, 42–44) reported on conventional systemic treatment. One article was prospective (43) and 3 retrospective (40, 42, 44). No articles were included on combination of 2 conventional systemic agents as this was an exclusion criteria in order to explore the true effectiveness of conventional systemic agents in daily practice. Except for one study on methotrexate (40), all studies reported a mean PASI score above 10 at start of treatment (11.6–26.5), which represents patients with moderate to severe psoriasis.

Acitretin

Study characteristics. One retrospective study (42) including 62 patients starting on acitretin was included. No prospective studies were available.
Monotherapy. In one retrospective study, PASI75 response was attained by 27% (42) of patients with a mean dose of 0.38 mg/kg/day at week 12. No prospective or retrospective data were available on long-term treatment with acitretin.

Fumarates

Study characteristics. Two articles (43, 44) reported the effectiveness of fumarates in daily practice, including a total of 312 patients starting on fumarates. One study was prospective and one (44) was retrospective. In one study (43) a maximum daily dose

of 360 mg was prescribed at week 6 and in the other study (44) this was 720 mg at week 9.

Monotherapy. One retrospective study showed a PASI75 of 47% (44) at week 12, 63% (44) at week 24, and 76% (44) at 1 year. No long-term results from prospective studies were available.

Cyclosporine

Study characteristics. One retrospective article (42) studied the effectiveness of cyclosporine in daily practice, including a total of 36 patients starting on cyclosporine. In this study, a mean dose of 3.5 mg/kg/day was given.

Monotherapy. In one retrospective study, 46% (42) of patients reached a PASI75 at week 12.

Methotrexate

Study characteristics. Three articles (40, 42, 44) studied the effectiveness of methotrexate in daily practice, including 189 patients starting on methotrexate. All studies were retrospective. In one study (40) the methotrexate dose was 15 mg weekly and was given intramuscularly. In another study (44) methotrexate initial dose of 10 mg once weekly was increased to a maximum of 20 mg once weekly. Piaserico et al. (42) gave methotrexate in a mean weekly dose of 11.7 mg.

Monotherapy. In the retrospective studies, between 40% and 49% (42, 44) of patients treated with methotrexate 10–20 mg weekly achieved PASI75 at week 12 and 62% (44) at week 24. Eighty-one percent (44) achieved PASI75 at 1 year. No prospective data were available.

Comparative studies

Three retrospective studies (40, 42, 44) and 2 prospective studies (18, 36) compared anti-psoriatic agents within the study. Piaserico et al. (42) showed that the proportion of patients achieving PASI75 with acitretin (27%) was significantly lower than that of patients treated with methotrexate (49%, $p = 0.01$), etanercept (64%, $p < 0.0001$), adalimumab (65%, $p < 0.01$) and infliximab (93%, $p < 0.001$) at week 12. Mean baseline PASI score appeared similar between these treatments (methotrexate: 12.7; acitretin 14.8; etanercept 14.9; adalimumab 14.3; infliximab 14.8). Inzinger et al. (44) showed that, when prescribed as a primary treatment, the effectiveness of methotrexate was similar to that of fumarates; however, the mean PASI at start of methotrexate (18.3) was higher than for fumarates (11.6). In this study, no significance tests were performed for baseline variables. Gisondi et al. (40) compared mean PASI decrease between methotrexate, etanercept and infliximab at week 24. Mean PASI decrease was significantly higher for infliximab compared with methotrexate, infliximab compared with etanercept, and etanercept compared with methotrexate.

Patients treated with etanercept or infliximab, however, had higher baseline PASI scores compared with patients receiving methotrexate ($p = 0.0001$). Between etanercept and infliximab treated patients, there was no significant difference in baseline PASI score ($p = 0.6$). The prospective study of Gisondi et al. (36) showed no significant differences between ustekinumab and infliximab for mean PASI decrease at weeks 4 and 28. Mean baseline PASI scores did not differ between these 2 groups ($p = 0.1$). The prospective study of Menting et al. (18) showed no significant difference in mean change in PASI scores between adalimumab, etanercept and infliximab at weeks 12 and 24. Baseline PASI did not differ between the 3 groups.

Discussion

To our knowledge, this is the first systematic review on effectiveness in daily practice of biologics (etanercept, adalimumab, infliximab and ustekinumab) and conventional systemic agents (acitretin, cyclosporine, fumarates and methotrexate). Effectiveness data from real-life, observational studies are of added value, since patients and treatment strategies in daily practice substantially differ from those in RCTs (8). A substantial proportion of patients were achieving PASI75 with short- (week 12–16), intermediate- (week 17–28) and long-term (≥ 1 year) treatment with biologics and conventional systemic agents, except for acitretin monotherapy.

At short-term, PASI75 was 35–68% for adalimumab, 12–66% for etanercept, 38–53% for infliximab, 63–80% for ustekinumab, 27% for acitretin, 47% for fumarates, 46% for cyclosporine and 40–49% for methotrexate. At long-term (1- and 2-year data), PASI75 was 44–89% for adalimumab, 49–92.3% for etanercept, 65.5% for ustekinumab, 76% for fumarates and 81% for methotrexate. We encountered a high heterogeneity in study design (prospective/retrospective), treatment regimen (e.g. dose adjustments, combination with conventional systemic agents) and patient population (e.g. baseline PASI scores, naïve/non-naïve) especially in studies on biologic treatments. Possible explanatory factors for the large ranges in PASI75 percentages, especially in etanercept and adalimumab therapy, were the use of combination strategies with a conventional systemic agent and dose adjustments.

In most studies on biologic therapies, concomitant conventional systemic agents were allowed and prescribed by physicians (24/29 studies). Methotrexate was mostly prescribed as combination therapy. In these studies, data were not analysed separately for patients using combination therapy. Therefore, we reported studies on combination therapy separately, but found similar PASI75 ranges between mono-therapy and combination therapy. There is some evidence from RCTs on combining biologics with conventional agents, with most data for etanercept combined with methotrexate (45). In daily clinical practice, however, combination strategies are often

applied in case of ineffectiveness, and may explain the similar results found in patients with and without combination therapies. More studies are needed into combination therapy of conventional systemic agents with biologic therapies.

Another explanation for the heterogeneity in study results is that dosing regimens differed between studies, especially for etanercept and adalimumab treatment. In adalimumab studies, all articles described dose increases and in studies with etanercept in more than half of included studies a dose increase was allowed. Aforementioned PASI75 results were therefore achieved with higher doses than licensed dose. Dose adjustments were less common in studies on infliximab and ustekinumab, although the number of included articles was too small to draw definitive conclusions. If this is indeed the case, dose adjustments could lead to higher costs for biologic treatment with etanercept and adalimumab compared with infliximab and ustekinumab.

Heterogeneity is typical in treating real-life patients and is not studied in RCTs. The results from daily practice studies enrich the body of evidence and can be of added value to current data from RCTs and guidelines when the quality of data reporting is improved. In order to improve this quality, it is strongly advised that authors of future studies report the items included in the STROBE statement (46). The following issues are of particular importance: study design (prospective, retrospective, wash-out period and method of analysis); and patient characteristics (age, sex, body weight, baseline PASI score, duration of psoriasis, previous treatments, presence of psoriatic arthritis, number of patients with and treatment duration of combinations of systemic anti-psoriatic therapies and dosages used). In case of biologic treatment in particular, it is important to describe naivety to biologics, previous biologic therapies, and dosing regimens.

Comparative studies were scarce and were hampered by differences at treatment start. Some RCTs (47–51) compared agents head-to-head. Data from pragmatic randomized daily practice studies or comparative effectiveness studies adjusted for confounders could be informative and decrease this gap in the evidence in the literature.

In conclusion, biologic and conventional systemic agents are effective in daily practice. Combination therapies of biologics with conventional systemic treatments and dose adjustments of biologics were frequently applied strategies, especially for adalimumab and etanercept, and could explain the large ranges in PASI75 results. There was a high heterogeneity in study design, treatment regimen and patient population between included studies. We made recommendations in order to improve the quality of reporting in daily practice studies. Gaps identified were daily practice data on infliximab, ustekinumab, conventional systemic therapies, long-term treatment, combination therapy and results of direct comparisons on effectiveness between anti-psoriatic agents.

Supplemental material

Table SI Inclusion and exclusion criteria

Inclusion criteria
Chronic plaque psoriasis Prospective or retrospective Thirty participants or more
Daily practice, database, registries, “real-world”, “real-life”, observational, cohort
Patients aged ≥ 18 years
English, Dutch or German language
Article reports on one of the following effectiveness outcomes: PASI, PhGA on a scale of 0–5, 0–6 or 0–7 or BSA
Reporting on the effectiveness of following treatments: adalimumab, etanercept, infliximab, ustekinumab, acitretin, fumarates, cyclosporine, or methotrexate
Reporting data analysed with the as-treated approach (per protocol analysis)
Exclusion criteria
Case reports
RCTs or clinical trials Safety studies
In vitro studies and other laboratory studies Pharmacokinetic studies
Cost-effectiveness studies
Open-label studies with a stringent protocol not reflecting daily practice Studies not reporting the time point at which effectiveness was measured Studies not reporting the dosage of treatment
Studies not reporting data separately per treatment
Studies reporting solely on non-systemic treatments such as phototherapy and topical therapies
Studies reporting solely on alefacept or efalizumab since these agents are no longer available for psoriasis treatment
Articles reporting on a combination of plaque psoriasis with other subtypes of psoriasis when the effectiveness data solely on chronic plaque psoriasis could not be extracted from the article
Studies describing only outcomes on psoriatic arthritis
Studies on specific psoriasis patient populations (e.g. psoriasis patients with HIV or hepatitis)
Studies in which conventional systemic agents were combined with other conventional systemic therapies
In patient cohorts treated with biologics, combination with conventional systemic was not excluded but described when appropriate

RCT: randomized controlled trial; PASI: Psoriasis Area and Severity Index; PhGA: Physician’s Global Assessment; BSA: body surface area.

Table SII Search strategy

Search strategy for PubMed and EMBASE:
Words that indicated daily practice and effectiveness:
"registry"; "database"; "daily practice"; "clinical practice"; "real-world"; "real-life"; "treatment outcome"; "observational"; "prospective"; "retrospective"; "PASI"; "PGA"; "BSA"
Combined with the treatments of interest:
"drug therapy"; "drug effects"; "therapeutic use"; "dermatologic agents"; "biological agents"; "tumour necrosis factor-alpha antagonists"; "anti-TNF"; "TNF- alpha inhibitors"; "antibodies monoclonal"; "antibodies monoclonal humanized"; "monoclonal antibody CA2"; "TNFR-Fc fusion protein"; "methotrexate"; "cyclosporine"; "acitretin"; "fumaric acid esters"; "fumarates"; "etanercept"; "adalimumab"; "infliximab"; "ustekinumab"

TNF: tumour necrosis factor; TNFR-Fc: tumour necrosis factor receptor (p75) Fc fusion protein; PASI: Psoriasis Area and Severity Index; PhGA: Physician's Global Assessment; BSA: body surface area.

Table SIII Evidence table

Available online: http://www.medicaljournals.se/acta/content/additional_content/4566SIIITab.pdf

References

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification, Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013; 133: 377-385.
2. Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. J Invest Dermatol 2014; 134: 1542-1551.
3. Grozdev I, Kast D, Cao L, Carlson D, Pujari P, Schmotzer B, et al. Physical and mental impact of psoriasis severity as measured by the compact Short Form-12 Health Survey (SF-12) quality of life tool. J Invest Dermatol 2012; 132:1111-1116.
4. Zweegers J, de Jong EM, Nijsten TE, de Bes J, te Booij M, Bogonjen RJ, et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatol Online J 2014; 20.
5. Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2014; 170: 274-303.
6. Puig L, Lopez A, Vilarrasa E, Garcia I. Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. J Eur Acad Dermatol Venereol 2014; 28 : 1633-1653.
7. Lucka TC, Pathirana D, Sammain A, Bachmann F, Rosumeck S, Erdmann R, et al. Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. J Eur Acad Dermatol Venereol 2012; 26: 1331-1344.
8. Garcia-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Dauden E, Sanchez-Carazo JL, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012; 148: 463-470.
9. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005; 64 Suppl 2: ii65-8; discussion ii9-73.
10. Frederiksson T, Petterson, U Severe psoriasis - oral therapy with a new retinoid. Dermatologica 1978: 238-244.
11. Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. J Invest Dermatol 2010; 130: 933-943.
12. Ryan C, Kirby B, Collins P, Rogers S. Adalimumab treatment for severe recalcitrant chronic plaque psoriasis. Clin Exp Dermatol 2009; 34: 784-788.
13. Van Lumig PP, Lecluse LL, Driessen RJ, Spuls PI, Boezeman JB, van de Kerkhof PC, et al. Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept. Br J Dermatol 2010; 163: 838-846.
14. Warren RB, Brown BC, Lavery D, Griffiths CE. Adalimumab for psoriasis: practical experience in a U.K. tertiary referral centre. Br J Dermatol 2010; 163: 859-862.
15. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Adalimumab for psoriasis in Greece: clinical experience in a tertiary referral centre. J Eur Acad Dermatol Venereol 2012; 26: 1298-1303.
16. Lopez-Ferrer A, Vilarrasa E, Gich IJ, Puig L. Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single Spanish centre. Br J Dermatol 2013; 169: 1141-1147.
17. van Lumig PP, van de Kerkhof PC, Boezeman JB, Driessen RJ, de Jong EM. Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naive vs. non-naive patients. J Eur Acad Dermatol Venereol 2013; 27: 593-600.
18. Menting SP, Sitaram AS, Bonnerjee-van der Stok HM, de Rie MA, Hooft L, Spuls PI. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. Br J Dermatol 2014; 171: 875-883.
19. de Groot M, Appelman M, Spuls PI, de Rie MA, Bos JD. Initial experience with routine administration of etanercept in psoriasis. Br J Dermatol 2006; 155: 808-814.

20. Berends MA, Driessen RJ, Langewouters AM, Boezeman JB, Van De Kerkhof PC, De Jong EM. Etanercept and efalizumab treatment for high-need psoriasis. Effects and side effects in a prospective cohort study in outpatient clinical practice. J Dermatolog Treat 2007; 18: 76-83.
21. Barrera MV, Habicheyn S, Mendiola MV, Herrera Ceballos E. Etanercept in the treatment and retreatment of psoriasis in daily clinical practice. Eur J Dermatol 2008; 18: 683-687.
22. Driessen RJ, Berends MA, Boezeman JB, van de Kerkhof PC, de Jong EM. Psoriasis treatment with etanercept and efalizumab: clinical strategies influencing treatment outcome. Br J Dermatol 2008; 158: 1098-1106.
23. Antoniou C, Dessinioti C, Stratigos A, Avgerinou G, Stavropoulos P, Katsambas A. Etanercept in severe, recalcitrant psoriasis: clinical response, safety profile and predictors of response based on a single institution's experience. J Eur Acad Dermatol Venereol 2009; 23: 979-982.
24. Driessen RJ, Boezeman JB, van de Kerkhof PC, de Jong EM. Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. Br J Dermatol 2009; 160: 670-675.
25. Jimenez-Puya R, Gomez-Garcia F, Amorrich-Campos V, Moreno-Gimenez JC. Etanercept: efficacy and safety. J Eur Acad Dermatol Venereol 2009; 23: 402-405.
26. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol 2009; 10:319-324.
27. Warren RB, Brown BC, Lavery D, Ashcroft DM, Griffiths CE. Biologic therapies for psoriasis: practical experience in a U.K. tertiary referral centre. Br J Dermatol 2009; 160: 162-169.
28. Antoniou C, Dessinioti C, Vergou T, Stratigos AJ, Avgerinou G, Kostaki M, et al. Sequential treatment with biologics: switching from efalizumab to etanercept in 35 patients with high-need psoriasis. J Eur Acad Dermatol Venereol 2010; 24: 1413-1420.
29. Zaragoza V, Perez A, Sanchez JL, Oliver V, Martinez L, Alegre V. [Long-term safety and efficacy of etanercept in the treatment of psoriasis]. Actas Dermosifiliogr 2010; 101: 47-53.
30. Antoniou C, Vergou T, Dessinioti C, Stratigos AJ, Avgerinou G, Stavropoulos P, et al. Etanercept: effectiveness and safety data of a retrospective study. J Eur Acad Dermatol Venereol 2011; 25: 1113-1115.
31. Esposito M, Giunta A, Mazzotta A, Zangrilli A, Babino G, Bavetta M, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. Dermatology 2012; 225: 312-319.
32. Van Lumig PP, Driessen RJ, Boezeman JB, Van De Kerkhof PC, De Jong EM. Long-term efficacy of etanercept for psoriasis in daily practice. Br J Dermatol 2012; 166: 445-447.
33. Puig L, Camacho Martinez FM, Gimeno Carpio E, Lopez-Avila A, Garcia-Calvo C. Efficacy and safety of clinical use of etanercept for the treatment of moderate-to-severe psoriasis in Spain: results of a multicentric prospective study at 12 months follow-up. Dermatology 2012; 225: 220-230.
34. Chiu HY, Wang TS, Cho YT, Tsai TF. Etanercept use for psoriasis in Taiwan: a case series study. Int J Dermatol 2013; 52:673-680.
35. van Lumig PP, Driessen RJ, Kievit W, Boezeman JB, van de Kerkhof PC, de Jong EM. Results of three analytical approaches on long-term efficacy of etanercept for psoriasis in daily practice. J Am Acad Dermatol 2013; 68: 57-63.
36. Gisondi P, Conti A, Galdo G, Piaserico S, De Simone C, Girolomoni G. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. Br J Dermatol 2013; 168: 1124-1127.
37. Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol 2011; 25: 1037-1040.
38. Laws PM, Downs AM, Parslew R, Dever B, Smith CH, Barker JN, et al. Practical experience of ustekinumab in the treatment of psoriasis: experience from a multicentre, retrospective case cohort study across the U.K. and Ireland. Br J Dermatol 2012; 166: 189-195.
39. Ruiz Salas V, Puig L, Alomar A. Ustekinumab in clinical practice: response depends on dose and previous treatment. J Eur Acad Dermatol Venereol 2012; 26: 508-513.

40. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: A retrospective cohort study. J Eur Acad Dermatol Venereol 2008; 22: 341-344.
41. Kalb RE, Gurske J. Infliximab for the treatment of psoriasis: clinical experience at the State University of New York at Buffalo. J Am Acad Dermatol 2005; 53: 616-622.
42. Piaserico S, Conti A, Lo Console F, De Simone C, Prestinari F, Mazzotta A, et al. Efficacy and safety of systemic treatments for psoriasis in elderly patients. Acta Derm Venereol 2014; 94: 293-297.
43. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. J Dermatolog Treat 2004; 15: 23-26.
44. Inzinger M, Weger W, Heschl B, Salmhofer W, Quehenberger F, Wolf P. Methotrexate vs. fumaric acid esters in moderate-to-severe chronic plaque psoriasis: data registry report on the efficacy under daily life conditions. J Eur Acad Dermatol Venereol 2013; 27: 861-866.
45. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. JAMA dermatology 2014; 150: 1213-1220.
46. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014; 12: 1495-1499.
47. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010; 362: 118-128.
48. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008; 158: 558-566.
49. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med 2014; 371: 326-338.
50. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol 2011; 164: 855-861.
51. Flytstrom I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol 2008; 158: 116-121.

6

Comparison of the one and 5-years effectiveness of adalimumab, etanercept and ustekinumab in patients with psoriasis in daily clinical practice

Results from the prospective BioCAPTURE registry

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Abstract

Background: The efficacy of etanercept and ustekinumab in psoriasis has been compared in one randomized controlled trial. Comparison of the long-term effectiveness of biologics in daily practice psoriasis treatment is currently lacking.

Objectives: To compare the effectiveness between the three widely used outpatient biologics adalimumab, etanercept and ustekinumab in daily practice psoriasis treatment and to correct for confounders.

Methods: Data were extracted from the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE). Multilevel linear regression analyses (MLRA) and generalized estimating equation (GEE) analyses were performed on, respectively, course of mean PASI and PASI75 (75% reduction of PASI compared with baseline). Both models were corrected for confounders. Subgroup analyses for biologic dose were performed.

Results: We included 356 patients with 513 treatment episodes; 178 adalimumab, 245 etanercept, 90 ustekinumab. MLRA showed a similar effectiveness between adalimumab, etanercept and ustekinumab after one year, but the highest effectiveness for ustekinumab during five years of treatment ($p=0.047$; ustekinumab versus etanercept $p=0.019$). GEE analysis revealed a higher chance of attaining PASI75 with adalimumab and ustekinumab compared with etanercept at one year of treatment. A higher than label dose was more often used in patients treated with etanercept (adalimumab, etanercept and ustekinumab: 31.5%, 55.1% and 16.7% after one year [$p<0.001$]; 39.3%, 71.4% and 24.4% after five years [$p<0.001$]).

Conclusions: Ustekinumab had the highest effectiveness during five years of treatment. Adalimumab and ustekinumab more often reached PASI75 than etanercept at one year of treatment. Etanercept was the agent most often prescribed in high doses.

Introduction

Biologics have revolutionized the treatments of psoriasis.[1] Randomized controlled clinical trials (RCTs) have shown that biologics are effective in treating selected patients with psoriasis.[2-10] In RCTs, a higher efficacy has been found for ustekinumab (USTE) compared with etanercept (ETA).[2] RCTs comparing USTE with adalimumab (ADA) or ETA with ADA have not been performed. Moreover, patients from RCTs differ from patients in daily practice and this might influence effectiveness of biologics in the real world.[11] Direct comparison of treatments in real-life setting is sparse. A recently performed systematic review[12] showed that two retrospective studies[13,14] and two prospective studies[15,16] were described that as a secondary objective compared the effectiveness of biologics in daily practice, but with short treatment periods (3-7 months), with few data on ustekinumab and uncorrected for baseline variables or other confounding factors. Long-term comparative real-world effectiveness data on biologic treatment for psoriasis, appropriately corrected for confounders, are currently lacking. This prospective daily practice study was performed in order to compare the effectiveness of the three widely used outpatient biologic treatments ADA, ETA and USTE by comparing mean Psoriasis Area and Severity Index (PASI)[17,18] decrease during the first five years of biologic treatment. Our secondary objective was to compare the mean PASI decrease as well as the PASI75 (75% reduction of PASI compared with baseline) between these agents, respectively, during the first year and at one year of treatment. All effectiveness analyses were corrected for confounders.

Methods

BioCAPTURE

Data were extracted from the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE)[19,20] for all patients from inception of the registry in 2005. This registry contains prospective daily practice data on all consecutive patients with psoriasis treated with biologics from one academic and eight non-academic centers. Patients were treated according to the guidelines[21,22] and recommendations were at the discretion of the attending dermatologist. When switching between biologics the newly introduced biologic was usually administered at the time point of the next scheduled drug dose of the previous biologic (for ADA after 2 weeks, for ETA after 1 week and for USTE after 12 weeks).[23] Dose adjustments, adjustments of treatment intervals and/or the addition of combination therapies with conventional systemic therapies were recorded. The registry was approved by our medical ethics committee. Informed consent was obtained from every patient.

Data collection and extraction

Outcomes

Data from patients were collected at baseline, week 6, week 12, then every three months until the first year of biologic treatment and thereafter every 3-6 months. PASI scores were extracted for all treatment episodes (TEs); the period in which a patient was treated with a certain biologic. In case the patient interrupted the biologic treatment for >90 days or if the patient switched to another biologic treatment, a new TE commenced. Ninety days is a widely accepted maximum interruption period.[20,24,25] One patient might, thus, have multiple TEs. TEs with at least a baseline PASI and one follow-up PASI at week 6 were included for analysis. Baseline PASI score was defined as PASI score at start or in case PASI was not recorded at that time point, the closest PASI between 90 days before and 7 days after the start of the biologic. The last PASI score was the PASI score at the stop date and if it was not recorded at that time point, the closest PASI until a maximum of 90 days after the stop date. Baseline patient characteristics, biologic treatment duration, the biologic dose and the use of concomitant systemic conventional therapy were extracted. Body Mass Index (BMI) was calculated from height and weight and expressed as kg/m^2.

Treatments

The cumulative biologic dose was calculated for every TE and subsequently this dose was divided by the expected cumulative dose if the patient would have been treated according to European Medicines Agency (EMA) label. Then, this ratio was expressed as a categorical variable (low-normal or high biologic dose compared with label dose, in which high dose represented a ratio >1). The mean biologic dose including the induction dose was used to present the dose per biologic group (ADA, ETA, USTE). The use of concomitant conventional therapies, such as acitretin, cyclosporine, fumarates and methotrexate was categorized into combination therapy or bridging therapy. Bridging therapy was defined as the use of a conventional systemic agent before the start of a biologic treatment until at least 28 days and for a maximum of 90 days after start of the biologic treatment. Combination therapy was defined as the start of a conventional systemic agent during biologic treatment with the conventional systemic agent being prescribed for at least 28 consecutive days. Exposure to a conventional systemic during biologic treatment was defined as bridging and/or combination therapy with a conventional systemic during the TE.

Statistical analysis

Analyses were performed using Microsoft Office Excel 2007, SPSS 22.0 (IBM, Armonk, NY, USA) and SAS 9.2 software (SAS Institute, Inc., Cary, NC). Variables with a normal distribution were presented as mean ± SD, non-normally distributed variables as median and inter-quartile range [IQR] and categorical data as N(%).

Baseline variables were compared between treatment groups using One-Way ANOVA in case of parametric and the Kruskal Wallis test in case of non-parametric distribution. Categorical variables were compared using the χ^2-test. Analysis on baseline characteristics was executed including multiple TEs from the same patient. A sensitivity analysis was performed on baseline variables in which only one TE per patient per treatment group was included. A P-value of 0.05 was considered significant.

For the primary analysis, multilevel linear regression analysis (MLRA) was performed to investigate differences between biologic treatments in mean PASI decrease over time during the first year and first five years of biologic treatment. With MLRA it is allowed to have repeated, correlated measurements, such as multiple TEs from the same patient.[26] In addition, a moment in time with very few observations will contribute little to the estimate of the treatment effect. Independent variables in this model were treatment and time. Firstly, a model was created including the interaction between time and biologic treatment to investigate whether a different pattern existed between the biologic agents over time. The pattern over time was irregular for all biologic agents and therefore a parallel-line model was created without the interaction term. In this model, residues were tolerably normally distributed and the requirement of homoscedasticity, i.e. similar variances of residuals at each level of the predictor variables, was reasonably met.

For the secondary analysis, PASI75 scores were calculated with the per protocol method[27] for Generalized Estimating Equation (GEE) analyses. GEE analysis allows to estimate parameters of a generalized linear model when the dependent variable is a dichotomous variable.[28] A GEE analysis can handle multiple TEs of patients. For GEE analysis it was only possible to include the first TE of the same biologic in case there were two TEs of the same biologic within the same patient. In addition a sensitivity analysis was performed calculating PASI75 using the last-observation-carried-forward (LOCF) method[27] in which the last available absolute PASI score was carried forward until 1 year of treatment.

Outcomes of all above mentioned analysis were corrected for confounders. Baseline variables that were considered as possible confounders were: age, sex, height, body weight, smoking status, alcohol use, family history of psoriasis, psoriatic arthritis, duration of psoriasis, baseline PASI score, prior biologic and prior TNF-α use. Those that were significantly different between the treatment groups were included in the MLRA and GEE as confounders and set as fixed variables.

The biologic dose expressed as low-normal or high compared with label dose and exposure to a concomitant conventional systemic therapy during a TE as well as the use of combination therapy were also compared between ADA, ETA and USTE treatment groups. When significantly different, subgroup analyses were performed.

Results

Patients

In total 513 TEs from 356 patients were included; ADA 178 TEs, ETA 245 TEs and USTE 90 TEs. For the MLRA all 513 TEs and for GEE analysis 483 TEs were included (Figure 1). Baseline patient characteristics, i.e. the characteristics of the patient at inclusion in BioCAPTURE, are shown in Table 1. The majority of patients were male (62.1%), overweight (BMI 27.4), smokers (74.2%) and had a positive family history of psoriasis (65.7%). Median baseline PASI score was 13.1. This is comparable to other major psoriasis patient registries.[29-31]

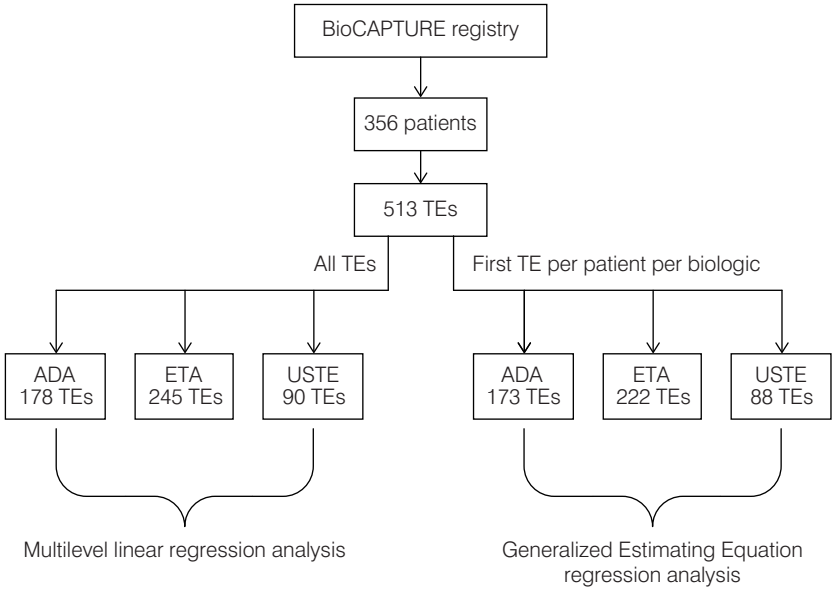
Baseline TE characteristics

Baseline characteristics of TEs are presented in Table 2; all TEs are included and therefore patients can appear more than once. Sensitivity analysis on baseline variables with one TE per patient per treatment group resulted in similar p-values as the p-values from analyses comparing baseline TE variables with multiple TEs (Table 2 and Supplement_Table 1). Median baseline PASI score was significantly higher for USTE (14.6) and ETA (13.0) compared with ADA (11.1; $p=0.001$ and $p<0.001$, respectively). Median baseline weight was significantly higher for USTE (92.0 kg) and ADA (88.0 kg) compared with ETA (82.8 kg; $p=0.001$ and 0.003, respectively). Other significantly different baseline TE characteristics were biologic naïvity ($p<0.001$), and anti-TNF- α naïvity ($p<0.001$; Table 2). Patients were significantly less often biologic naïve and anti-TNF-α naïve in TEs of USTE compared with ADA ($p= 0.003$ and $p=0.009$, respectively) and ETA ($p<0.001$ in both analyses). All significantly different baseline characteristics were incorporated into the MLRA and GEE analysis to correct for their possible confounding effect.

Treatment characteristics

Treatment characteristics during the first year and first five years of biologic treatment are shown in Table 3. Only the biologic dose expressed as low-normal or high was statistically significantly different between biologics after one and five years. Ever exposure to a conventional systemic as well as combination therapy were not significantly different between the biologics. A description of biologic dose, bridging and combination therapy in our cohort can be found in the Supplement and Supplement_Table 2.

Figure 1 Flow chart of included patients into MLRA and GEE analyses



Patients treated with ADA, ETA or USTE from BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics).

TE = treatment episode

Effectiveness

Course of mean PASI

The mean PASI decrease of ADA, ETA and USTE during five years, uncorrected for confounders, is visualized in Figure 2A. Mean baseline PASI score differed between the agents (ADA 11.6 ± 5.8; ETA 14.7 ± 8.2; USTE 15.1 ± 8.0). It is shown that ADA, ETA and USTE treatment resulted in a rapid decrease in mean PASI during the first three months. After one year of treatment mean PASI decrease seemed to stabilize for all three biologics (Figure 2A). Uncorrected for confounders, Figure 2A gives the impression that ADA and USTE show better responses compared with ETA at one year and five years of treatment. This impression remains when only correcting for baseline PASI score (Supplement_Figure 1).

Table 1 Baseline patient characteristics

Baseline patient characteristics	***First ever TE in BioCAPTURE N=356***
Age at start of biologic (yrs)	47.6 ± 12.7 *Missing: 0*
Gender (male)	221 (62.1%) *Missing: 0*
Length (cm)	175.5 ± 8.8 *Missing: 82*
Weight (kg)	84.6 [22.1] *Missing: 78*
BMI (kg/m^2)	27.4 [6.6] *Missing: 82*
Smoking status, present or past (yes)	264 (74.2%) *Missing:6*
Alcohol use, present or past (yes)	255 (71.6%) *Missing: 9*
Positive family history of psoriasis (yes)	234 (65.7%) *Missing: 12*
Psoriatic arthritis, diagnosis by a Rheumatologist (yes)	104 (29.2%) *Missing: 18*
Duration of psoriasis until start of biologic (yrs)	19.6 [17.1] *Missing: 2*
Baseline PASI score	13.1 [8.0] *Missing: 0*

Mean ± SD, Median [IQR], N(%).

Since a high biologic dose was more often prescribed in ETA treated patients, followed by ADA and then USTE, effectiveness was split for low-normal dosed TEs and high dosed TEs (Figure 2B; uncorrected for confounders). From this figure, it can be seen that all high dosed TEs remained at a higher PASI when compared with low dosed TEs.

Table 2 Baseline characteristics of included treatment episodes (TEs)

Baseline TE characteristics	***Adalimumab N= 178 TEs***	***Etanercept N= 245 TEs***	***Ustekinumab N= 90 TEs***	***p***
Age at start of biologic (yrs)	49.0 ± 12.4 *Missing: 0*	47.1 ± 12.8 *Missing: 0*	49.3 ± 12.5 *Missing: 0*	0.208†
Gender (male)	103 (57.9%) *Missing: 0*	152 (62.0%) *Missing: 0*	58 (64.4%) *Missing: 0*	0.523¥
Length (cm)	175.6 ± 8.6 *Missing: 16*	175.2 ± 8.0 *Missing: 76*	176.6 ± 8.6 *Missing: 8*	0.478†
Weight (kg)	88.0 [24.9] *Missing: 16*	82.8 [24.3] *Missing: 75*	92.0 [21.1] *Missing: 4*	*0.001*‡
BMI (kg/m^2)	29.2 [6.5] *Missing: 17*	27.1 [6.5] *Missing: 76*	28.6 [6.4] *Missing: 8*	*0.002*‡
Smoking status, present or past (yes)	135 (75.8%) *Missing: 2*	185 (75.5%) *Missing: 4*	67 (74.4%) *Missing: 1*	0.958¥
Alcohol use, present or past (yes)	126 (70.8%) *Missing: 4*	172 (70.2%) *Missing: 4*	63 (70%) *Missing: 2*	0.972¥
Positive family history of psoriasis (yes)	121 (68%) *Missing: 5*	159 (65.0%) *Missing: 7*	59 (65.6%) *Missing: 3*	0.796¥
Psoriatic arthritis (yes)	55 (30.9%) *Missing: 7*	72 (29.4%) *Missing: 4*	23 (25.6%) *Missing: 9*	0.330¥
Duration of psoriasis until start of biologic (yrs)	20.4 [18.4] *Missing: 2*	20.4 [17.7] *Missing: 0*	18.43 [13.8] *Missing: 0*	0.667‡
Baseline PASI score	11.1 [7.5] *Missing: 0*	13.0 [7.9] *Missing: 0*	14.6 [12.2] *Missing: 0*	*<0.001*‡
Biologic naïve (yes)	63 (35.4%) *Missing: 0*	147 (60.0%) *Missing: 0*	16 (17.7%) *Missing: 0*	*<0.001*¥
Anti-TNF-α naïve (yes)	70 (39.3%) *Missing: 0*	170 (69.4%) *Missing: 0*	21 (23.3%) *Missing: 0*	*<0.001*¥

Mean ± SD, Median [IQR], N(%). N/A = Not applicable
† One-Way ANOVA, ¥ chi-squared test, ‡ Kruskal Wallis test

Table 3 Treatment characteristics of included treatment episodes (TEs) at one and five years of biologic treatment.

Treatment characteristics-first year of treatment	***Adalimumab N= 178 TEs***	***Etanercept N= 245 TEs***	***Ustekinumab N= 90 TEs***	***p***
Cumulative dose of biologic (mg)	991 ± 376	3001 ± 1070	268 ± 108	N/A
Time average dose of biologic (mg/day)	3.5 ± 0.8	10.4 ± 2.5	0.9 ± 0.3	N/A
Dose higher than EMA label during TE (yes)	56 (31.5%) *Missing: 0*	135 (55.1%) *Missing: 0*	15 (16.7%) *Missing: 0*	*<0.001*¥
Exposure to a conventional systemic agent during TE (yes)	47 (26.4%) *Missing: 0*	58 (23.7%) *Missing: 0*	16 (17.8%) *Missing: 0*	0.291¥
Combination therapy without bridging during TE (yes)	37 (20.8%) *Missing: 0*	44 (18.0%) *Missing: 0*	14 (15.6%) *Missing: 0*	0.554¥
Treatment characteristics-first 5 years of treatment	***Adalimumab N= 178 TEs***	***Etanercept N= 245 TEs***	***Ustekinumab N= 90 TEs***	***p***
Cumulative dose of biologic (mg)	2627 ± 2199	9611 ± 8407	604 ± 555	N/A
Average dose of biologic (mg/day)	3.4 ± 0.9	9.9 ± 2.6	0.9 ± 0.3	N/A
Dose higher than EMA label during TE (yes)	70 (39.3%) *Missing: 0*	175 (71.4%) *Missing: 0*	22 (24.4%) *Missing: 0*	*<0.001*¥
Exposure to a conventional systemic agent during TE (yes)	50 (28.1%) *Missing: 0*	64 (26.1%) *Missing: 0*	18 (20.0%) *Missing: 0*	0.353¥
Combination therapy without bridging during TE (yes)	40 (22.5%) *Missing: 0*	50 (20.4%) *Missing: 0*	16 (17.8%) *Missing: 0*	0.663¥
Combination or bridging with conventional agent	Total: 52 c.s. Combi: 42 (81%) Bridging: 10 (19%)	Total: 72 c.s. Combi: 57 (79%) Bridging: 15 (21%)	Total: 20 c.s. Combi: 18 (90%) Bridging: 2 (10%)	N/A
Concomitant conventional systemic drugs (combination or bridging; number of agents)	Methotrexate: 40 Cyclosporine: 7 Acitretin: 4 Fumarates: 1	Methotrexate: 42 Cyclosporine: 11 Acitretin: 14 Fumarates: 3 Tacrolimus: 1 MMF: 1	Methotrexate: 14 Cyclosporine: 1 Acitretin: 5 Fumarates: 0	N/A

Mean ± SD, N(%), N/A = Not applicable. C.s. = conventional systemic. MMF: mycophenolate mofetil.
¥ chi-squared test

Five year effectiveness - Course of mean PASI

Over 5 years of treatment, MLRA showed a significant difference between medication (p=0.047) with overall the most favorable effectiveness results for USTE compared with ETA (p=0.019). There were no significant differences between the other biologic groups (Supplement_Table 3).

Split for biologic dose, effectiveness of the low-normal dosed TEs of ADA, ETA and USTE was comparable as was the effectiveness of high dosed TEs (Supplement_ Table 3).

One year effectiveness - Course of mean PASI

Overall, MLRA showed no significant differences between ADA, ETA and USTE during the first year of treatment (Supplement_Table 3). Also, no significant differences were encountered in the low-normal dosed TEs between biologics. Numerically, however, ADA and USTE performed better than ETA in both overall effectiveness and the effectiveness of low-normal doses.

One year effectiveness - PASI75

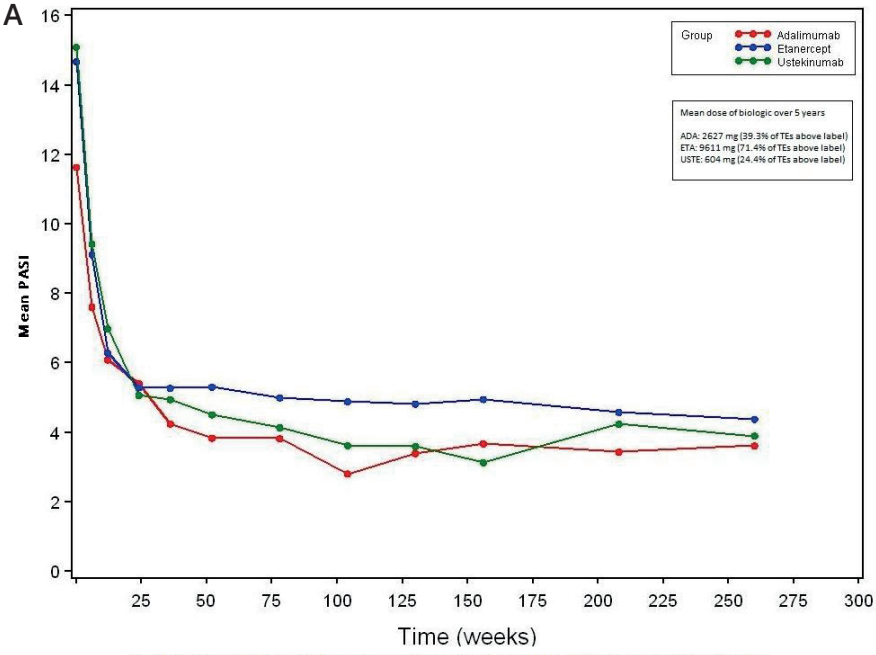
Per-protocol PASI75 data uncorrected for confounders for the first year of treatment are visualized in Supplement_Figure 2. The uncorrected PASI75 percentages were ETA 39.1%, ADA 45.9% and USTE 45.3% after one year of treatment. Uncorrected PASI75 data for low-normal dosed TEs during the first year of treatment are shown in Supplement_Figure 3. This figure represents the percentage of low-normal dosed TEs in which a PASI75 was reached, from the total group of low-normal dosed TEs.

GEE analysis on per-protocol data showed that, overall, ADA and USTE had a higher chance in achieving a PASI75 compared with ETA at one year of treatment (Supplement_Table 3, overall p=0.028; ADA vs ETA p=0.010; USTE vs ETA p= 0.048). Sensitivity analysis on PASI75 LOCF data showed that USTE was better than ADA and ETA (Supplement_GEE_LOCF, Supplement_Figures 4&5).

GEE subanalysis of low-normal dosed TEs showed that ADA had a higher chance than ETA, but not USTE in reaching PASI75 (Supplement_Table 3; ADA vs ETA p=0.011; ADA vs USTE p=0.546; USTE vs ETA p=0.111). Sensitivity analysis on LOCF data showed that USTE was better than ETA, but not better than ADA (Supplement_GEE_LOCF, Supplement_Figures 4&5).

Figure 2A and B Mean PASI from baseline until 5 years of biologic treatment (as treated analysis), uncorrected for confounders, and split for low-normal and high dosed TEs

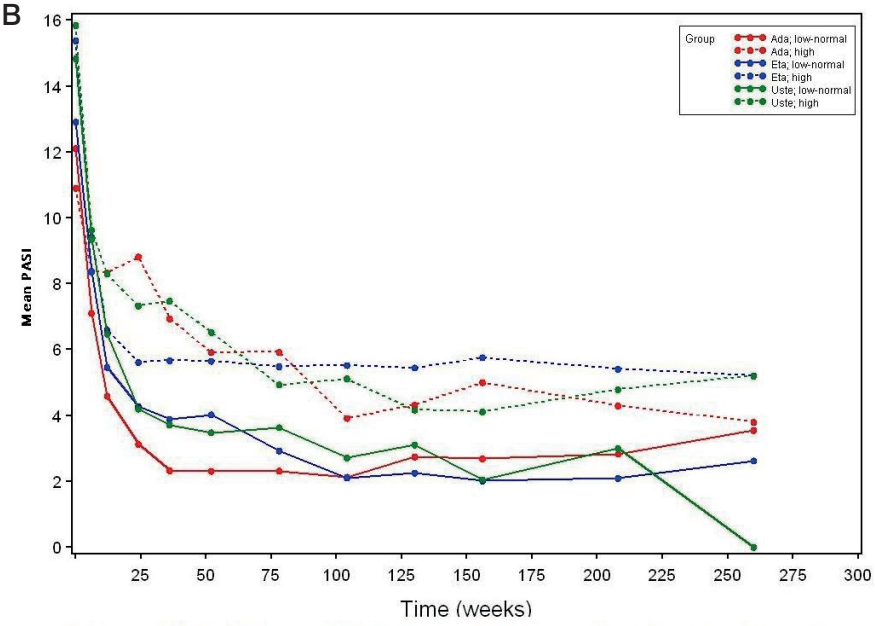
A



Mean (+/-SD) PASI values from baseline until 5 years of biologic treatment (as treated analysis) uncorrected for confounders

	Adalimumab			Etanercept			Ustekinumab		
Time (years)	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
0	11.6	5.8	178	14.7	8.2	245	15.1	8.0	90
0.5	5.4	6.2	147	5.3	4.9	190	5.1	4.5	73
1	3.8	4.4	111	5.3	4.4	156	4.5	4.1	53
2	2.8	2.3	66	4.9	3.5	107	3.6	2.8	29
3	3.7	3.7	49	5.0	4.0	79	3.0	2.2	19
4	3.4	2.8	29	4.6	3.1	60	4.0	2.6	13
5	3.6	2.7	14	4.4	2.9	47	3.9	3.8	4

B



Split for low-normal and high dosed TEs: the mean(+/-SD) PASI values and number of patients from baseline until 5 years of biologic treatment (as treated analysis) uncorrected for confounders

	Adalimumab low-normal dosed TEs			Adalimumab high dosed TEs			Etanercept low-normal dosed TEs			Etanercept high dosed TEs			Ustekinumab low-normal dosed TEs			Ustekinumab high dosed TEs		
Time (yrs)	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
0	12.1	6.2	108	10.9	5.2	70	12.9	7.0	70	15.4	8.6	175	14.8	7.5	68	15.9	9.4	22
0.5	3.1	4.2	88	8.8	7.2	59	4.3	4.3	46	5.6	5.0	144	4.2	4.3	52	7.3	4.4	20
1	2.3	2.3	64	5.9	5.6	47	4.0	4.0	33	5.7	4.4	123	3.5	2.9	35	6.5	5.5	18
2	2.1	1.7	41	3.9	2.8	25	2.1	1.0	20	5.5	3.6	87	2.7	2.5	18	5.1	2.5	11
3	2.7	1.9	28	5.0	5.0	21	2.0	1.3	17	5.8	4.2	62	2.1	1.8	9	4.1	2.1	10
4	2.8	1.9	17	4.3	3.6	12	2.1	1.2	15	5.4	3.1	45	3.0	3.9	4	4.8	2.0	9
5	3.6	3.1	10	3.8	1.6	4	2.6	1.2	15	5.2	3.1	32	0	N/A	1	5.2	3.5	3

ADA= adalimumab, ETA= etanercept, USTE= ustekinumab. Low-normal= actual dose was low to normal compared with the expected label dose during the treatment episode. High= actual dose was higher than the expected label dose during the treatment episode. Notice the difference in mean baseline PASI between the different dosing groups.

Discussion

This prospective, multicenter study provides the comparative effectiveness between ADA, ETA and USTE in real-life treatment of patients with psoriasis. USTE had the highest overall effectiveness during the first five years of treatment. During the first year of treatment USTE and ADA had a higher chance of attaining PASI75 compared with ETA.

No major differences existed between ADA, ETA and USTE in the course of mean PASI in low-normal doses during one and five year treatment. Thus, in case low-normal doses of biologics were maintained during this study, all biologics had a similar effectiveness. Physicians were, however, less often able to maintain a low-normal dose in ETA treated patients, followed by ADA and then USTE. Also, all high dosed TEs remained at a higher PASI when compared with low dosed TEs. High doses of biologics were thus prescribed to a subpopulation of patients with psoriasis with a suboptimal response to biologic therapy. Hence, a suboptimal response was more often the case in ETA treated patients, followed by ADA and then USTE. Therefore, USTE was the drug with the highest overall effectiveness in daily clinical practice during five years of treatment. Data from other prospective patient registries are needed to verify these observations.

High doses of ADA, ETA and USTE were equally effective over 5 years of treatment. High dosed patients, however, remained at a higher mean PASI when compared with low dosed patients. Currently, knowledge about the effect of dose adjustments in daily practice is scarce.[12] Studies on the effect of dose adjustments of the different biologics are needed to aid the physician in deciding whether to adjust the biologic dose or switch to another biologic agent.

Dose adjustments were most frequently made in ETA, followed by ADA and lastly USTE treatment. The observation that in ETA and ADA treatment dose is more frequently adjusted when compared with USTE corresponds to a recent systematic review.[12] Although more TEs of ETA had a higher dosing regimen when compared with ADA and USTE, it did not result in a more successful mean PASI course during long-term five years treatment.

That USTE is an effective agent has been shown in RCTs[2,6,7,32] with USTE being more effective than ETA[2]. Recent real-world data show that USTE has the highest first-course drug survival, which is a comprehensive measure of effectiveness, safety, and patients' and doctors' preferences[24,33]. In addition, results from our study indicate that USTE might be the preferred agent for long-term psoriasis treatment.

Differences in effectiveness results between biologics might be explained by the difference in mode of action between anti-TNF-α receptor blocker ETA, anti-TNF-α antibody ADA and the anti-IL12/IL23 antibody USTE. USTE, by blocking IL-12 and IL-23, reduces the survival and proliferation of, respectively, Th1 and Th17 cells.

Especially Th17 cells play a key role in the development of psoriasis.[34] It can be hypothesized that USTE exhibits a higher effectiveness compared with TNFα-inhibitors due to the fact that the IL-12 and IL-23 cytokines function more downstream in the cascade of cytokines involved in the immunopathogenesis of psoriasis compared with the TNF-α cytokine.[1,35] It is also known, however, that not every patient reaches the same effectiveness results, which in theory could be explained by the activation of different sets of genes between patients.[36] More research is needed to explain why differences in effectiveness are seen between biologic agents and between patients.
A limitation of our study is that patient adherence to biologics was not measured, for example with patient questionnaires. The exact dose with which patients are treated might therefore vary from the calculated dose. Dose adjustments were, however, recorded in our registry and data showed that dose adjustments were indeed given to a patient group with suboptimal responses to therapy. Another limitation might be that we used PASI75 as an outcome measure for our secondary objective instead of PASI 90/100. The number of patients reaching PASI90/100 was, however, insufficient for sound analysis in our study. Research with cohorts including larger numbers of patients could answer this question. Strengths of our study include the similarity of our patients with other major registries, the prospective nature and multicenter character of the study, the inclusion of long-term PASI data and biologic doses as well as correcting all analyses for confounders. Another strength is the use of MLRA that provides us with an estimate of the effect of USTE that is only little influenced by the low number of TEs of USTE at the end of five-year treatment.
This is the first prospective, real-world study in which effectiveness data, i.e. course of mean PASI and PASI75, from the first five years of biologic treatment are compared between the three most commonly prescribed outpatient biologics ADA, ETA and USTE corrected for confounders in patients with psoriasis that were comparable to other major psoriasis patient registries. Our data show that, amongst outpatient biologics, USTE is the most effective agent in daily practice during five years of psoriasis treatment. When the physician was able to keep the patient on a low-normal biologic dose the effectiveness between the outpatient biologics was similar. Patients on low-normal doses had lower mean PASI scores compared with high dosed patients. Keeping a low-normal dose was most often the case in USTE treated patients which resulted in USTE being the most effective agent in psoriasis treatment in daily practice. When high doses were needed, a similar effectiveness was seen between biologics during long-term treatment. These findings warrant replication from other prospective daily practice cohorts and further research into dose adjustments of biologics in the real-world.

Supplemental material

Supplement_Table 1 Baseline and treatment characteristics of included treatment episodes (one TE per patient per treatment group)

Baseline TE characteristics	***Adalimumab N= 173 TEs***	***Etanercept N= 222 TEs***	***Ustekinumab N= 88 TEs***	***p-value***
Age at start of biologic (yrs)	48.8 ± 12.5 *Missing: 0*	47.0 ± 12.8 *Missing: 0*	49.5 ± 12.4 *Missing: 0*	0.184†
Gender (male)	100 (57.8%) *Missing: 0*	140 (63.1%) *Missing: 0*	56 (63.6%) *Missing: 0*	0.500¥
Length (cm)	175.5 ± 8.6 *Missing: 16*	175.1 ± 8.1 *Missing: 67*	176.6 ± 8.7 *Missing: 8*	0.411†
Weight (kg)	87.3 [23.7] *Missing: 16*	82.5 [24.8] *Missing: 66*	92.0 [21.2] *Missing: 4*	*0.001*‡
BMI (kg/m^2)	29.0 [6.5] *Missing: 17*	27.1 [6.3] *Missing: 67*	28.6 [6.7] *Missing: 8*	*0.003*‡
Smoking status (yes)	132 (76.3%) *Missing: 2*	168 (75.7%) *Missing: 3*	65 (73.9%) *Missing: 1*	0.902¥
Alcohol use (yes)	122 (70.5%) *Missing: 4*	158 (71.2%) *Missing: 3*	62 (70.5%) *Missing: 2*	1.000¥
Positive family history of psoriasis (yes)	118 (68.2%) *Missing: 5*	142 (64.0%) *Missing: 6*	57 (64.8%) *Missing: 3*	0.642¥
Psoriatic arthritis (yes)	55 (31.8%) *Missing: 7*	68 (30.6%) *Missing: 4*	22 (25.0%) *Missing: 9*	0.252¥
Duration of psoriasis until start of biologic (yrs)	20.3 [18.5] *Missing: 2*	20.7 [17.3] *Missing: 0*	18.43 [14.0] *Missing: 0*	0.691‡
Baseline PASI score	11.2 [7.2] *Missing: 0*	13.3 [8.3] *Missing: 0*	14.8 [12.2] *Missing: 0*	*<0.001*‡
Biologic naïve (yes)	63 (36.4%) *Missing: 0*	147 (66.2%) *Missing: 0*	16 (18.2%) *Missing: 0*	*<0.001*¥
Anti-TNF-α naïve (yes)	70 (40.5%) *Missing: 0*	170 (76.6%) *Missing: 0*	21 (23.9%) *Missing: 0*	*<0.001*¥
Treatment characteristics during the first 5 years of treatment	***Adalimumab N= 173 TEs***	***Etanercept N= 222 TEs***	***Ustekinumab N= 88 TEs***	***p-value***
Dose higher than EMA label during TE (yes)	68 (39.3%) *Missing: 0*	159 (71.6%) *Missing: 0*	20 (22.7%) *Missing: 0*	*<0.001*¥
Conventional systemic agent ever exposed during TE (yes)	50 (28.9%) *Missing: 0*	60 (27.0%) *Missing: 0*	18 (20.5%) *Missing: 0*	0.334¥
Combination therapy without bridging during TE (yes)	40 (23.1%) *Missing: 0*	47 (21.2%) *Missing: 0*	16 (18.2%) *Missing: 0*	0.652¥

Mean ± SD, Median [IQR], N(%). N/A = Not applicable.
† One-Way ANOVA, ¥ chi-squared test, ‡ Kruskal Wallis test

Supplement_*Biologic dose*

After one year of treatment, a higher dose than EMA label was significantly more often prescribed in TEs of ETA (n=135; 55.1%) compared with ADA (n=56; 31.5%) and USTE (n=15; 16.7%; p<0.001, Table 3). After five years of treatment, TEs of ETA had still significantly the highest percentage of TEs with a higher dose than label (n=175 TEs; 71.4%), followed by ADA (n=70 TEs; 39.9%) and USTE (n=22 TEs; 24.4%; ETA vs ADA p<0.001; ETA vs USTE p<0.001; ADA vs USTE p=0.015). Most commonly, high doses were doses adjustments to 75 or 100 mg weekly for ETA, 40mg weekly for ADA, interval decrease for USTE 45mg and a dose increase of USTE to 90mg per 12 weeks. The cumulative dose and the average daily dose of the biologics as well as their expected label doses are presented in Table 4. This table shows that the mean doses of biologics in daily practice are higher than label dose for every biologic, but highest for ETA, followed by ADA and USTE. Dose of USTE was lower than expected after the first year of treatment (eTable 2). After 5 years of treatment, the mean dose of ETA including the induction dose was 72.1 ± 17.8 mg per week (low-normal dosed TEs 61.2 ± 17.4 mg per week; high dosed TEs 76.4 ± 16.0 mg per week). Mean dose of ADA with induction dose was 49.2 ± 12.0 mg per two weeks (low-normal dosed TEs 43.8.± 8.9 mg per two weeks; high dosed TEs 57.5 ± 11.5 mg per two weeks) and mean dose of USTE with induction dose was 71.5 ± 26.5 mg per 12 weeks (low-normal dosed TEs 45mg and 90mg group, respectively: 57.3 ± 15.7 mg and 107.0 ± 15.0 mg per 12 weeks; high-dosed TEs 45mg and 90mg group, respectively: 79.8 ± 22.6 mg and 125.0 ± 5.4 mg per 12 weeks).

Supplement_*Combination and bridging therapy*

After one and five years, ever exposure to a conventional systemic agent (i.e., bridging and/or combination therapy) or combination therapy with a conventional systemic agent were equally distributed amongst biologic treatment groups (Table 3). After 5 years, 50 (28.1%), 64 (26.1%) and 18 (20.0%) TEs of ADA, ETA and USTE, respectively, were ever exposed to a conventional systemic agent in the form of bridging and/or combination therapy. Bridging therapy occurred in 10 (19%), 15 (21%) and 2 (10%) TEs of ADA, ETA and USTE. Combination therapy was prescribed in 40 (22.5%), 50 (20.4%) and 16 (17.8%) TEs of respectively ADA, ETA and USTE. One TE of ETA had a bridging as well as one combination therapy. The number of conventional systemic agents prescribed as combination therapies and their percentage of the total of conventional systemic agents in the biologic treatment group were 42 (81% of 52), 57 (79% of 72) and 18 (90% of 20) in ADA, ETA and USTE treatment, respectively. In one TE of ADA, four TEs of ETA and two TEs of USTE the patients received more than one combination treatment during the five year period (ADA: 1TE two times a combination; ETA: 2 TEs 2 times a combination, 1 TE 3 times a combination, 1 TE 4 times a combination; USTE: 2 TEs 2 times a combination treatment).

Supplement_Table 2 Mean doses and mean expected label doses of the biologics

Mean doses	*Adalimumab N= 178 TEs*		*Etanercept N= 245 TEs*		*Ustekinumab N= 90 TEs*	
First year of treatment	*Observed data*	*Expected per label*	*Observed data*	*Expected per label*	*Observed data*	*Expected per label*
Cumulative dose of biologic (mg)	991 ± 376 (7% increase compared with expected)	922 ± 312	3001 ± 1070 (11% increase compared with expected)	2703 ± 701	268 ± 108 (-12% increase compared with expected)	303 ± 126
Time average dose of biologic (mg/day)	3.5 ± 0.8	3.2 ± 0.5	10.4 ± 2.5	9.5 ± 1.4	0.9 ± 0.3	1.0 ± 0.4
First 5 years of treatment	*Observed data*	*Expected per label*	*Observed data*	*Expected per label*	*Observed data*	*Expected per label*
Cumulative dose of biologic (mg)	2627 ± 2199 (13% increase compared with expected)	2327 ± 1812	9611 ± 8407 (22% increase compared with expected)	7892 ± 6690	604 ± 555 (13% increase compared with expected)	536 ± 392
Time average dose of biologic (mg/day)	3.4 ± 0.9	3.2 ± 0.5	9.9 ± 2.6	8.8 ± 1.9	0.9 ± 0.3	0.8 ± 0.3

Mean ± SD

Supplement_Table 3 Results from the multilevel linear regression analysis (MLRA) and generalized estimating equation (GEE) analysis for adalimumab (ADA), etanercept (ETA) and ustekinumab (USTE) over 1 and 5 years of treatment.

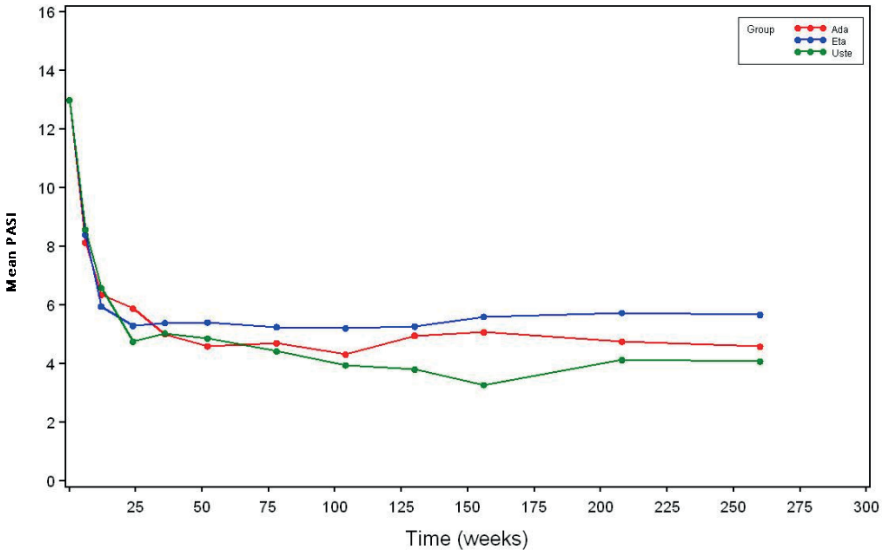
For MLRA, results are presented as mean PASI over time with 95% confidence interval.

For GEE, results are presented as odds ratio with 95% confidence interval.

5 years MLRA	***ADA***	***ETA***	***USTE***	***p***
Overall	5.2 [4.6-5.8]	5.9 [5.4-6.5]	4.7 [3.9-5.5]	*0.047*
Low-normal dosed TEs	4.1 [3.4-4.8]	5.0 [3.9-6.1]	4.3 [3.3-5.2]	0.341
High dosed TEs	6.9 [6.0-7.8]	6.1 [5.5-6.8]	5.6 [4.2-7.0]	0.171
1 year MLRA	***ADA***	***ETA***	***USTE***	***p***
Overall	5.8 [5.2-6.4]	6.4 [5.8-7.0]	5.3 [4.5-6.2]	0.128
Low-normal dosed TEs	4.6 [4.0-5.2]	5.6 [4.7-6.4]	4.9 [4.0-5.7]	0.185
1 year GEE	***ADA***	***ETA***	***USTE***	***p***
Overall	1.03 [0.5-2.1]	0.43 [0.19-0.99]	1.0‡	*0.028*
Low-normal dosed TEs	1.30 [0.55-3.07]	0.43 [0.15-1.21]	1.0‡	*0.040*

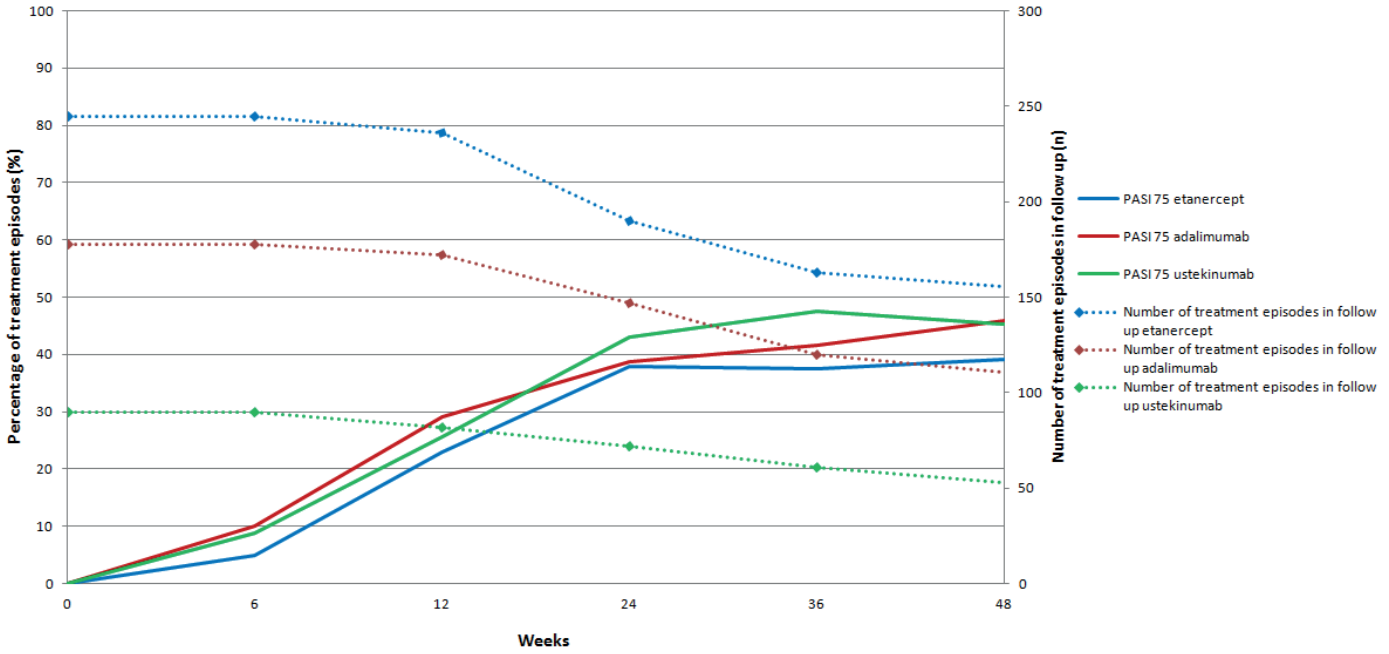
‡ Set to 1.0 in order to compare other biologics with USTE.

Supplement_Figure 1 Mean PASI over time according to multilevel linear regression analysis only corrected for baseline PASI score

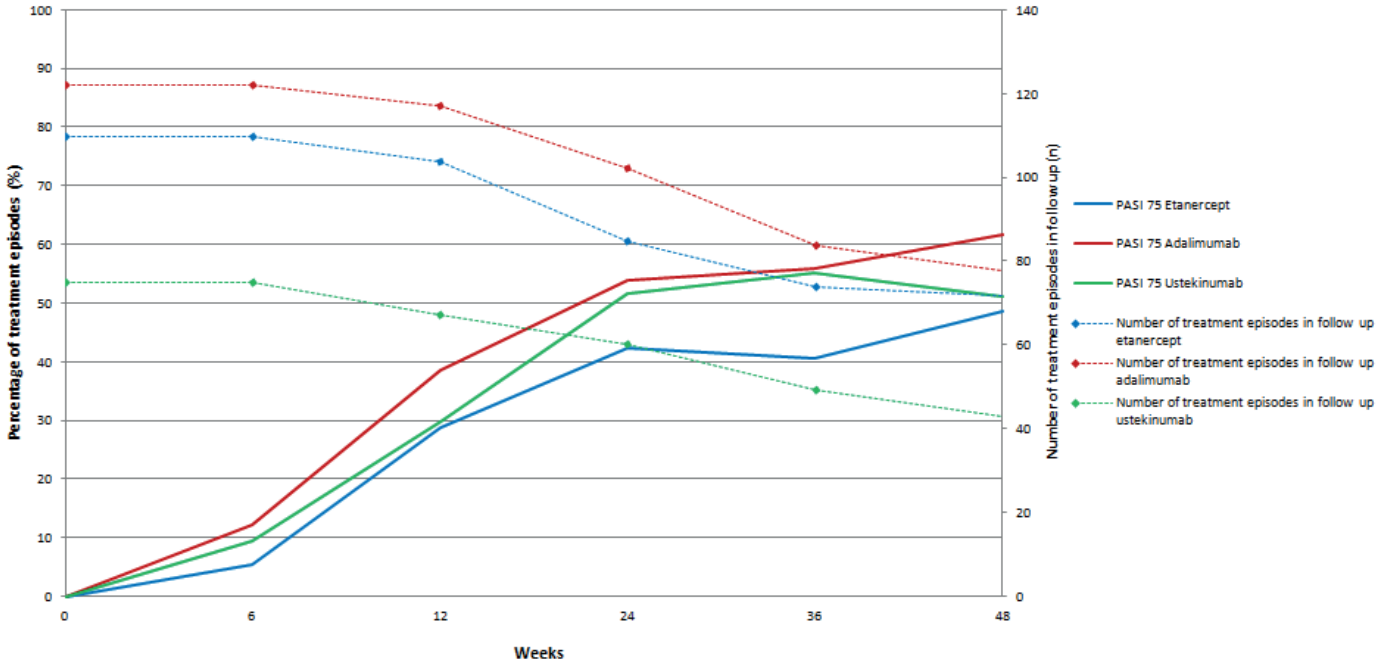


Mean baseline PASI set at 13.0. Ada = Adalimumab; Eta = Etanercept; Uste = Ustekinumab.

Supplement_Figure 2 Uncorrected one-year PASI75 percentages of adalimumab, etanercept and ustekinumab (per protocol analysis)



Supplement_Figure 3 Uncorrected one-year PASI75 percentages of adalimumab, etanercept and ustekinumab for low-normal dosed TEs (per protocol analysis)

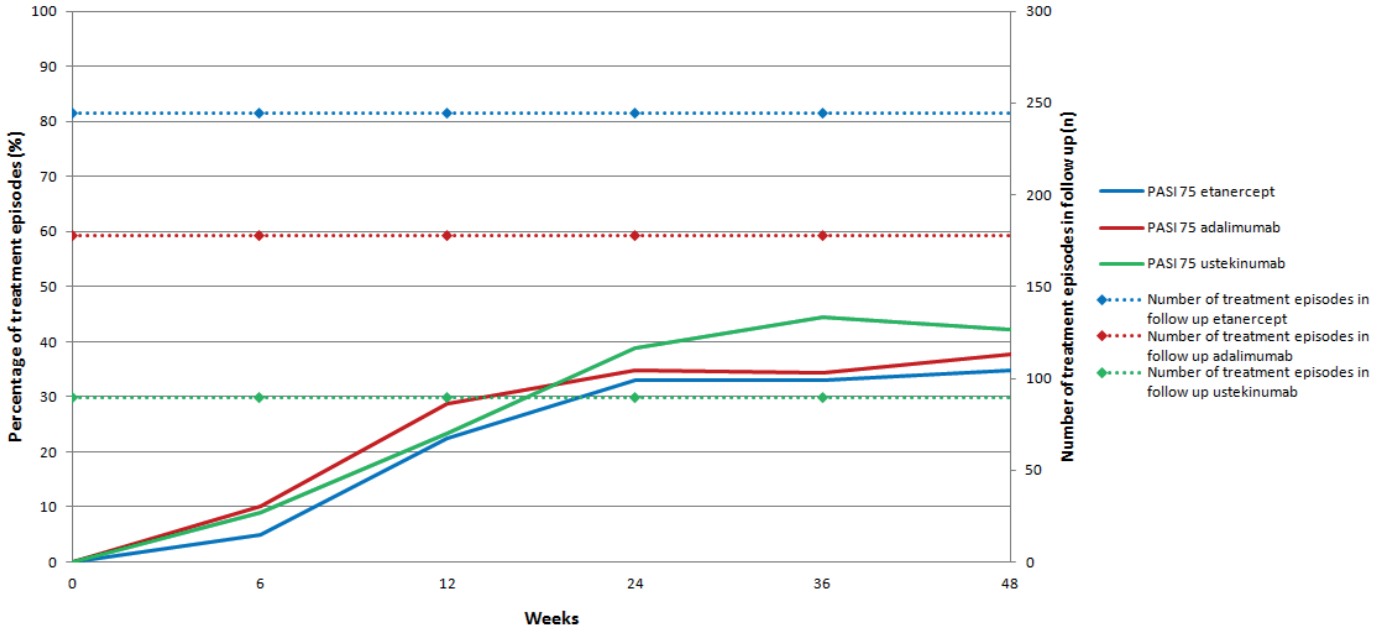


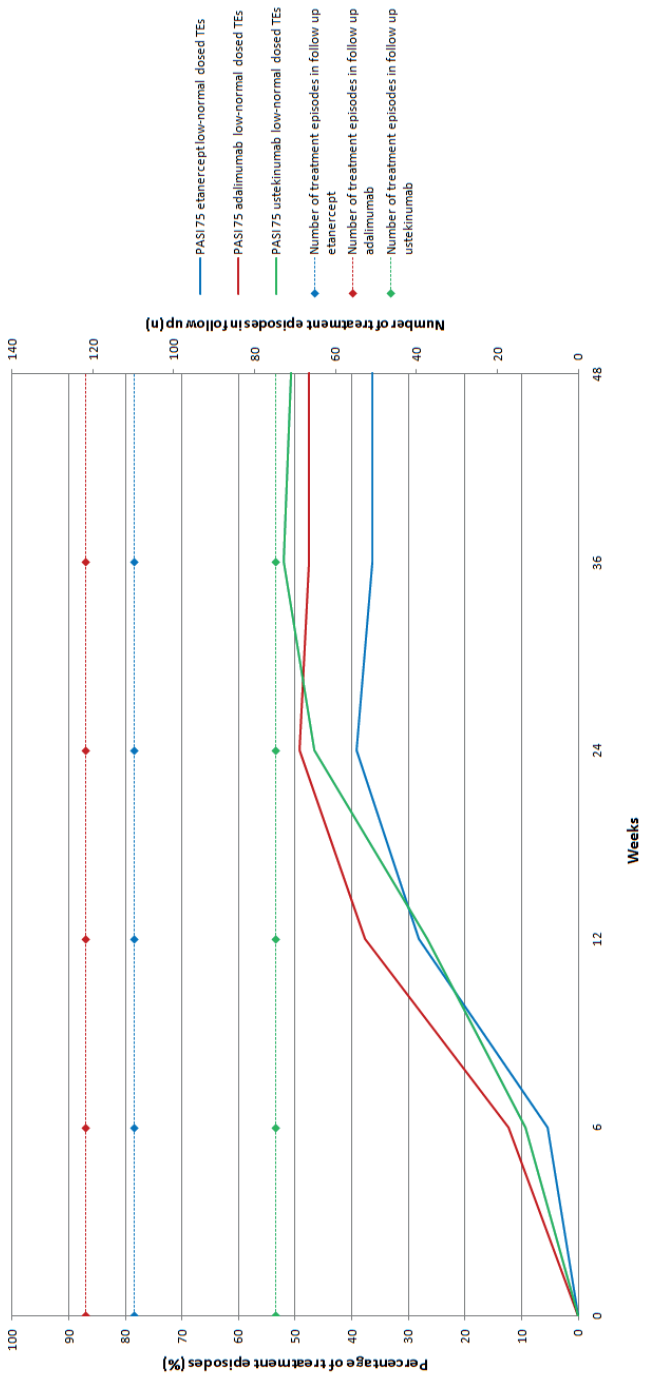
Supplement_*GEE_LOCF*

Generalized Estemating Equation regression analysis, last-observation-carried-forward analysis

Last-observation-carried-forward PASI75 data uncorrected for confounders during the first year of treatment is visualized in Supplement_Figure 4. The uncorrected PASI75 for ETA was 34.7%, ADA 37.6% and USTE 42.2% at one year of treatment. GEE analysis showed a significant difference in favor of USTE compared with ADA and ETA in attaining PASI75 after one year of treatment (p=0.014; ADA 0.56; ETA 0.38; USTE 1.0; USTE vs ETA p=0.004; USTE vs ADA p=0.049; ADA vs ETA p=0.159). Uncorrected PASI75 data for low-normal dosed TEs are shown in Supplement_Figure 5. This figure represents the percentage of low-normal dosed TEs in which a PASI75 was reached, from the total group of low-normal dosed TEs. The uncorrected PASI75 for low-normal dosed ETA was 36.4%, ADA 47.5% and USTE 50.7% at one year of treatment. In the low-dosed TEs, GEE analysis showed that USTE was more effective than ETA in achieving PASI75 (p=0.033; ADA 0.65, ETA 0.34, USTE 1.00; USTE vs ETA p=0.009; USTE vs ADA p=0.195; ADA vs ETA p=0.069).

Supplement_Figure 4 Uncorrected one-year PASI75 percentages of adalimumab, etanercept and ustekinumab (last-observation-carried-forward analysis)





Supplement_Figure 5 Uncorrected one-year PASI75 percentages of adalimumab, etanercept and ustekinumab for low-normal dosed TEs (last-observation-carried-forward analysis)

References

1 Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496-509.
2 Griffiths CE, Strober BE, van de Kerkhof P et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010; 362: 118-28.
3 Leonardi CL, Powers JL, Matheson RT et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003; 349: 2014-22.
4 Gordon KB, Langley RG, Leonardi C et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006; 55: 598-606.
5 Chaudhari U, Romano P, Mulcahy LD et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001; 357: 1842-7.
6 Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1665-74.
7 Papp KA, Langley RG, Lebwohl M et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008; 371: 1675-84.
8 Leonardi C, Matheson R, Zachariae C et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med 2012; 366: 1190-9.
9 Langley RG, Elewski BE, Lebwohl M et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med 2014; 371: 326-38.
10 Krueger JG, Ferris LK, Menter A et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2015.
11 Garcia-Doval I, Carretero G, Vanaclocha F et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012; 148: 463-70.
12 Zweegers J, Otero ME, van den Reek JM et al. Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review. Acta Derm Venereol 2015.
13 Gisondi P, Cotena C, Tessari G et al. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: A retrospective cohort study. J Eur Acad Dermatol Venereol 2008; 22: 341-4.
14 Piaserico S, Conti A, Lo Console F et al. Efficacy and safety of systemic treatments for psoriasis in elderly patients. Acta Derm Venereol 2014; 94: 293-7.
15 Gisondi P, Conti A, Galdo G et al. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. Br J Dermatol 2013; 168: 1124-7.
16 Menting SP, Sitaram AS, Bonnerjee-van der Stok HM et al. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. Br J Dermatol 2014; 171: 875-83.
17 Frederiksson T, Petterson, U Severe psoriasis - oral therapy with a new retinoid. . Dermatologica 1978: 238-44.
18 Sofen H, Smith S, Matheson RT et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol 2014; 133: 1032-40.
19 Zweegers J, van den Reek JM, van de Kerkhof PC et al. Comparing treatment goals for psoriasis with treatment decisions in daily practice: results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE. Br J Dermatol 2014; 171: 1091-8.
20 van den Reek JM, Zweegers J, Kievit W et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. Br J Dermatol 2014; 171: 1189-96.

21 Zweegers J, de Jong EM, Nijsten TE et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatol Online J 2014; 20.
22 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009; 23 Suppl 2: 1-70.
23 Mrowietz U, de Jong EM, Kragballe K et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2014; 28: 438-53.
24 Warren RB, Smith CH, Yiu ZZ et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol 2015.
25 Esposito M, Gisondi P, Cassano N et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. Br J Dermatol 2013; 169: 666-72.
26 Dickinson LM, Basu A. Multilevel modeling and practice-based research. Ann Fam Med 2005; 3 Suppl 1: S52-60.
27 van Lumig PP, Driessen RJ, Kievit W et al. Results of three analytical approaches on long-term efficacy of etanercept for psoriasis in daily practice. J Am Acad Dermatol 2013; 68: 57-63.
28 Liang K-Y, Zeger SL. Longitudinal Data Analysis Using Generalized Linear Models. Biometrika 1986; 73: 13-22.
29 Hagg D, Eriksson M, Sundstrom A et al. The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. PLoS One 2013; 8: e63619.
30 Reich K, Mrowietz U, Radtke MA et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. Arch Dermatol Res 2015.
31 Menter A, Thaci D, Papp KA et al. Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. J Am Acad Dermatol 2015; 73: 410-9 e6.
32 Langley RG, Lebwohl M, Krueger GG et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol 2015; 172: 1371-83.
33 van den Reek JM, Kievit W, Gniadecki R et al. Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls. J Invest Dermatol 2015; 135: e34.
34 Koutruba N, Emer J, Lebwohl M. Review of ustekinumab, an interleukin-12 and interleukin-23 inhibitor used for the treatment of plaque psoriasis. Ther Clin Risk Manag 2010; 6: 123-41.
35 Gaspari AA, Tyring S. New and emerging biologic therapies for moderate-to-severe plaque psoriasis: mechanistic rationales and recent clinical data for IL-17 and IL-23 inhibitors. Dermatol Ther 2015; 28: 179-93.
36 Prieto-Perez R, Cabaleiro T, Dauden E et al. Genetics of psoriasis and pharmacogenetics of biological drugs. Autoimmune Dis 2013; 2013: 613086.

7

Frequency of and predictors for a high clinical response in patients with psoriasis on biologic therapy in daily practice

Results from the prospective, multicenter BioCAPTURE cohort

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Abstract

Background: It is important to assess which patients with psoriasis are more likely to achieve high clinical responses on biologics in daily practice.

Objectives: To assess the number of treatment episodes (TEs) that reach PASI100 (100% reduction in Psoriasis Area and Severity Index), PASI90 or PASI≤5 at week 24 of biologic treatment, and which baseline patient characteristics predict treatment response.

Methods: Data from patients with psoriasis treated with adalimumab, etanercept, infliximab or ustekinumab were extracted from a prospective cohort. Percentages of TEs with high clinical responses were described. Univariate and multivariate regression analyses were performed with the Generalized Estimating Equation method with patient as random effect to elucidate which baseline patient characteristics were predictors for PASI90 and PASI≤5 at week 24.

Results: In total, 454 TEs were included (159 adalimumab; 193 etanercept; 19 infliximab; 83 ustekinumab) from 326 patients. At week 24, in 3%, 15% and 59% of TEs, respectively, PASI100, PASI90 and PASI≤5 was reached. In TEs without PASI100 or PASI90 response, PASI≤5 was still achieved in a substantial proportion (58% and 52% respectively). Baseline PASI≥10 was a strong predictor for reaching PASI90; baseline PASI<10 and a lower baseline BMI were significant predictors for PASI≤5 at week 24.

Conclusions: In daily practice, a limited number of patients reached PASI100 or PASI90 at 24 weeks of biologic treatment. We showed the importance of including an absolute PASI score in the assessment of psoriasis severity. Baseline BMI was an important, modifiable predictor for a high response on biologics for psoriasis.

Introduction

A 90% improvement of the Psoriasis Area and Severity Index (PASI90) is more and more observed with current therapies for psoriasis. PASI90 corresponds better with a clear or almost clear psoriasis and with a good quality of life compared with PASI75.[1-3] Therefore, treatment success in psoriasis is starting to shift from PASI75 to PASI90.[1] A high clinical response can be defined as reaching a relative PASI measure such as PASI90 or PASI100, but can also be described by reaching a low absolute PASI score such as PASI≤5. Studies show that a good quality of life is also more often achieved in patients with an absolute PASI≤5 compared with PASI>5.[1,4,5] The difference between relative and absolute PASI might be important in the treatment of patients with psoriasis in daily practice, in which patients with high baseline PASI scores (PASI≥10) but also with lower baseline PASI scores (PASI<10) are being treated with biologics. A lower baseline PASI score might occur in patients that switch from one biologic treatment to another. It is more difficult to achieve PASI90 in patients with a low PASI score at start of treatment compared with patients with high baseline PASI scores. With this study our first research objective was to assess how many patients with psoriasis that were treated with biologics in daily practice for 24 weeks, reached a high clinical response (PASI90, PASI100, PASI≤5) at week 24. Secondly, we wanted to assess how many patients that achieved PASI90 at week 24 also reached PASI≤5 at week 24. Thirdly, it was assessed how many patients without PASI90 or PASI100 response, still achieved PASI≤5 at week 24.

Baseline patient characteristics might predict whether a psoriasis patient will reach a high clinical response (PASI90, PASI100 or PASI≤5) on biologic treatment. To date, no studies have tried to assess which patients with psoriasis are more likely to achieve these high clinical responses. Predicting a high clinical response is, however, important for personalized treatment and can also increase the awareness of physicians for those patients at risk of not achieving a high clinical response. Moreover, knowledge on predictors might direct future research, such as randomized controlled trials (RCTs) that will try to improve the efficacy of biologics for those patients that are not expected to reach a high clinical response based on these predictors. Baseline patient characteristics associated with the effectiveness of biologics in previous studies were baseline body mass index (BMI), baseline severity score, duration of psoriasis and biologic naivity.[6-9] Our secondary objective was to assess which patients were more likely to achieve a high clinical response by analysing which baseline patient characteristics were predictors for high clinical response at 24 weeks of treatment with biologics. For our research objectives, we used prospective daily practice registry data from BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics).[10]

Methods

BioCAPTURE

BioCAPTURE is a registry containing prospective, multicenter data on biologic treatment of patients with plaque psoriasis from daily practice.[10] This registry contains prospective daily practice data on all consecutive patients with psoriasis treated with biologics from one academic and eight non-academic centers. BioCAPTURE was approved by the medical ethics committee. Informed consent was obtained from every patient. Treatment of patients with psoriasis occurs according to European and Dutch guidelines.[11,12] Treatment decisions, such as dose adjustments, were made by the treating physician.

Data extraction

Data from patients with psoriasis that were treated with biologics (adalimumab [ADA], etanercept [ETA], infliximab [IFX] and ustekinumab [USTE]) were extracted from BioCAPTURE (2005 – May 2015). Extracted baseline variables were PASI score, age at start of biologic, sex, weight, length, BMI, psoriatic arthritis, positive family history of psoriasis, duration of psoriasis until start of biologic and biologic naivity. A treatment episode (TE) was defined as a period of time in which the patient received a biologic without interrupting treatment for >90 days. Ninety days is a widely accepted interruption period.[13-15] The baseline PASI score of a TE was defined as PASI score at start or if it was not recorded at that time point, the closest PASI between 90 days prior to and 7 days after the start of the biologic. For each patient, only the first TE per biologic was chosen if a patient had received the same biologic twice. One patient could have multiple TEs when the patient had switched from one biologic to a different biologic agent. The mean average biologic dose during the first 24 weeks was calculated. It was also calculated whether the total biologic dose during the first 24 weeks of treatment was low to normal or higher than European Medicines Agency (EMA) label dose. In addition, it was extracted whether during a TE a concomitant conventional systemic agent (methotrexate [MTX]; acitretin [NT]; fumaric acid esters [FAE]; cyclosporine [CyA]) was prescribed in the first 24 weeks of biologic treatment. Bridging and combination therapy were both regarded as the prescription of a concomitant conventional agent.

Analyses

Patients that discontinued the biologic treatment due to ineffectiveness before week 24, were considered non-responders (not achieving PASI90, PASI100 and PASI≤5) at week 24. Data from patients who discontinued due to other reasons, such as adverse events or pregnancy whish, were not included in the analyses. To optimize power, all biologics were grouped together. The time point to evaluate whether treatment

success is being achieved differs between biologics, but an evaluation at 24 weeks of treatment seems appropriate for biologics.[16,17] Firstly, percentages of TEs in which PASI90, PASI100 or PASI≤5 were reached at week 24 were described. Then, the percentage of TEs in which PASI90 and PASI≤5 was reached at week 24 as well as the percentage of TEs in which PASI90 or PASI100 was not achieved but in which PASI≤5 was still achieved at week 24 were calculated. Thereafter, the percentage of TEs with a baseline PASI≥10 in which PASI90, PASI100 and PASI≤5 was reached at week 24 was described. Lastly, univariate (Supplement_Table 1) and multivariate regression analyses were performed to elucidate which baseline patient characteristics were predictors for PASI90 or PASI≤5 at week 24. Baseline PASI score was divided into baseline PASI≥10 and <10. Due to low numbers of TEs in which PASI100 was achieved (15 TEs; 3.3%) at week 24, predictors for this outcome could not be assessed. Since one patient could contribute to multiple TEs, the Generalized Estimating Equation (GEE) analysis with patient as random effect was chosen in order to analyze which baseline patient variables predicted PASI90 and PASI≤5. A GEE analysis takes into account the patients that are included more than once in the analysis. With GEE analysis, parameters of a generalized linear model are estimated when the dependent variable is a dichotomous variable.[18] After the univariate analyses with GEE, baseline patient variables with a p-value of <0.2 were incorporated into the multivariate analyses. Backward selection was manually performed by stepwise excluding the baseline patient variable with the highest p-value above 0.05. The final predictor model included those baseline patient variables that had a p-value of <0.05. For the multivariate analyses, BMI was chosen over weight, since these variables highly correlated. Sensitivity analyses with weight instead of BMI were performed. Additional sensitivity analyses were performed for (1) ADA/ETA as a group (excluding IFX and USTE), (2) TEs with a low to normal label biologic dose, (3) TEs without a treatment interruption, (4) TEs without combination therapy and (5) PASI≤3 at week 24 because in all TEs with a PASI90 at week 24 an absolute PASI score of ≤3 was present. Correction for missing baseline data was performed using multiple imputations in SPSS. Predictors were described as (B [95% confidence interval]; p-value). Analyses were performed using Microsoft Office Excel 2007 and SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Patients

Table 1 shows the characteristics of the 326 included patients from BioCAPTURE. Our cohort was comparable to other major daily practice psoriasis registries[19,20]; most patients with psoriasis treated with biologics were male (62.0%), overweight (27.6 kg/m^2) and had a positive family history of psoriasis (67.5%). Median baseline PASI score was 12.8.

Table 1 *Baseline patient characteristics of BioCAPTURE*

Baseline patient characteristics	***N=326***
Age at start of biologic (yrs)	47.2 ± 12.6 *Missing: 0*
Gender (male)	202 (62.0%) *Missing: 0*
Length (cm)	175.6 ± 8.7 *Missing: 62*
Weight (kg)	86.4 [23.0] *Missing: 60*
BMI (kg/m^2)	27.6 [6.8] *Missing: 62*
Positive family history of psoriasis (yes)	214 (67.5%) *Missing: 9*
Psoriatic arthritis, diagnosis by a Rheumatologist (yes)	97 (31.1%) *Missing: 14*
Duration of psoriasis until start of biologic (yrs)	20.3 [17.2] *Missing: 2*
Baseline PASI score	12.8 [8.1] *Missing: 0*

Mean ± SD, Median [IQR], N(%).

Baseline characteristics of treatment episodes

In total, 483 TEs were extracted of which 454 TEs were included; 159 ADA, 193 ETA, 19 IFX and 83 USTE. Baseline characteristics of TEs are shown per biologic in Table 2. Thirty-seven of 454 TEs did not complete 24 weeks due to ineffectiveness, and were included into the analyses as non-responders. Since no comparisons between biologics were made, no statistical comparisons between baseline characteristics

Table 2 Baseline characteristics of included treatment episodes (TEs).

Baseline TE characteristics	***Adalimumab N= 159 TEs***	***Etanercept N= 193 TEs***	***Infliximab N= 19 TEs***	***Ustekinumab N= 83 TEs***
Age at start of biologic (yrs)	48.9 ± 12.5 *Missing: 0*	47.0 ± 12.5 *Missing: 0*	49.3 ± 12.9 *Missing: 0*	50.4 ± 12.6 *Missing: 0*
Sex (male)	94 (59.1%) *Missing: 0*	124 (64.2%) *Missing: 0*	10 (52.6%) *Missing: 0*	54 (65.1%) *Missing: 0*
Length (cm)	175.7 ± 8.7 *Missing: 14*	175.1 ± 8.0 *Missing: 52*	173.8 ± 8.4 *Missing: 0*	177.0 ± 8.8 *Missing: 4*
Weight (kg)	88.0 [23.1] *Missing: 14*	82.5 [24.5] *Missing: 52*	92.0 [21.8] *Missing: 0*	91.3 [21.2] *Missing: 2*
BMI (kg/m^2)	29.0 [6.5] *Missing: 15*	26.7 [6.2] *Missing: 52*	30.5 [7.1] *Missing: 0*	28.1 [6.3] *Missing: 4*
Positive family history of psoriasis (yes)	107 (67.3%) *Missing: 4*	128 (66.3%) *Missing: 5*	11 (57.9%) *Missing: 1*	54 (65.1%) *Missing: 2*
Psoriatic arthritis (yes)	54 (34.0%) *Missing: 6*	57 (29.5%) *Missing: 3*	11 (57.9%) *Missing: 0*	22 (26.5%) *Missing: 6*
Duration of psoriasis until start of biologic (yrs)	20.8 [18.5] *Missing: 2*	21.0 [16.9] *Missing: 0*	16.4 [11.3] *Missing: 1*	18.6 [14.5] *Missing: 0*
Baseline PASI score	11.1 [7.6] *Missing: 0*	12.6 [8.3] *Missing: 0*	14.5 [11.8] *Missing: 0*	13.6 [12.3] *Missing: 0*
Biologic naïve (yes)	53 (33.3%) *Missing: 0*	126 (65.3%) *Missing: 0*	0 (0%) *Missing: 0*	15 (18.1%) *Missing: 0*

Mean ± SD, Median [IQR], N(%).

were performed. Numerically, median baseline PASI score was highest for patients that were treated with IFX (14.5) and lowest for patients on ADA (12.0). Of 454 TEs, 67.4% (306/454) of TEs had a baseline PASI≥10 and 32.6% (148/454) of TEs had a baseline PASI<10. Median baseline weight was highest for patients on IFX (92.0kg), followed by USTE (91.3kg), ADA (88.0kg) and lastly ETA (82.5kg). In our cohort, IFX was the last resort treatment; all patients that were treated with IFX were biologic non-naïve.

Treatment characteristics of treatment episodes

The treatment characteristics of TEs are shown in Supplement_Table 2. The median biologic dose including induction dose was 46 mg per 2 weeks for ADA, 72 mg per week for ETA, 7.6 mg/kg/8 weeks for IFX and 62mg per 12 weeks for USTE (USTE 45mg group: 62 mg per 12 weeks; USTE 90mg group: 123 mg per 12 weeks). In 17.6%, 45.1% and 10.8% of TEs of, respectively, ADA, ETA and USTE, the biologic dose was higher than would be expected by EMA label dose after 24 weeks of treatment. Two (12.5%) of 16 TEs that started with 90mg USTE received a starting dose higher than label (i.e., in these 2 TEs body weight was ≤100kg) and 9 (13.4%) of 67 TEs that started with 45mg USTE received a starting dose lower than label (i.e., in these 9 TEs body weight was >100kg). All doses of IFX were per EMA label. Biologics were combined with conventional systemic agents in 114 TEs, varying from bridging therapy to continuous combination therapy. MTX was the agent most often prescribed. Of 454 TEs, in 95 (20.9%) TEs treatment was interrupted with a total of 114 treatment interruptions. Time of interruption was usually short (in 97 interruptions ≤4 weeks; in 17 interruptions >4 weeks). The median time of treatment interruption was 9.5 [interquartile range (IQR): 14] days.

High clinical response

The number and percentages of TEs in which high clinical responses were achieved, are shown in Table 3 and Figure 1.

PASI100 at week 24: In only 3.3% (15/454) of TEs, PASI100 was reached at week 24. In all TEs (100%) with PASI100 response at week 24, PASI≤5 was also attained at week 24. Of the 439 TEs without PASI100 response, in still 57.6% (253/439) PASI≤5 was reached at week 24. From 306 TEs with a baseline PASI≥10, in 3.9% (12/306) PASI100 was reached at week 24. In 2% (3/148) of TEs with a baseline PASI<10, PASI100 was achieved at week 24.

PASI90 at week 24: In 15% (67/454) of TEs PASI90 was attained at week 24. In all TEs (100%) with PASI90 response at week 24, PASI≤5 was also attained at week 24. In all TEs (100%) with PASI90 at week 24, PASI≤3 was achieved at week 24. An absolute PASI score of 2.7 was the highest absolute PASI score in the PASI90 group. Of the 387 TEs without PASI90 response, in still 51.9% (201/387) PASI≤5 was reached at

week 24. From 306 TEs with a baseline PASI≥10, in 19.0% (58/306) of TEs PASI90 was reached at week 24. In only 6.1% (9/148) of TEs with a baseline PASI<10, PASI90 was achieved at week 24.

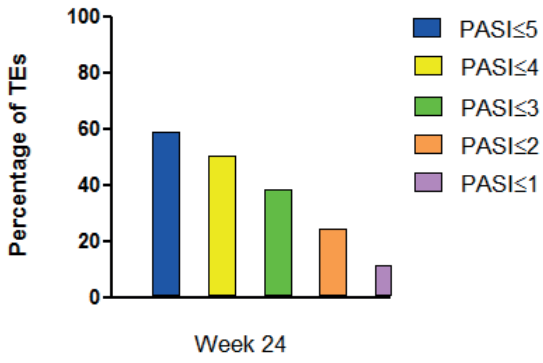
PASI≤5 at week 24: Of 454 TEs, in 268 (59.0%) TEs PASI≤5 was reached at week 24. From 306 TEs with a baseline PASI≥10, in 54.6% (167/306) of TEs PASI≤5 was achieved at week 24. This was 68.2% (101/148) of TEs with a baseline PASI<10. In 50.2%, 38.5%, 24.2% and 11.2% of 454 TEs, respectively, PASI≤4, PASI≤3, PASI≤2 and PASI≤1 was reached at week 24 (Figure 1).

Table 3 Treatment episodes (TEs) reaching PASI100, PASI90 or PASI≤5 at week 24

Outcome	*Number of TEs that reached the outcome at week 24 N (% of all TEs in study)*	*Number of TEs that did not reach the outcome at week 24 N (% of all TEs in study)*	*Number of TEs that reached outcome and also reached PASI≤5 at week 24 N (% of TEs that reached outcome)*	*Number of TEs that did not reach outcome, but still reached PASI≤5 at week 24 N (% of TEs that did not reach outcome)*
PASI100	15 (3.3%)	439 (96.7%)	15 (100%)	253 (57.6%)
PASI90	67 (14.8%)	387 (85.2%)	67 (100%)	201 (51.9%)
PASI≤5	268 (59.0%)	186 (41.0%)	268 (100%)	0 (0%)

Total number of TEs in study: 454.

Figure 1 Percentage of treatment episodes (TEs) with high effectiveness based on absolute PASI scores at week 24



Total number of TEs in study: 454.

Predictors for high clinical response

After correcting for multiple TEs from the same patients with multivariate GEE regression analysis, the most important predictor for reaching a PASI90 response at week 24 was baseline PASI≥10 (baseline PASI≥10: 1.284 [0.541-2.027]; p=0.001). Predictors for PASI≤5 at week 24, were baseline PASI<10 and a lower baseline BMI (baseline PASI<10: 0.555 [0.161-0.949]; p=0.006 and BMI: -0.068 [-0.108- -0.028]; p=0.001).

Sensitivity analyses for PASI≤3 at week 24, revealed the same predictors as the analyses for PASI≤5. Sensitivity analyses on ADA/ETA as one group (excluding IFX and USTE), also resulted in the same predictors for PASI90, PASI≤5 and PASI≤3. Sensitivity analyses with weight instead of BMI showed that baseline PASI remained the only predictor for PASI90 at week 24 (baseline PASI≥10: 1.284 [0.541-2.027]; p=0.001). For PASI≤5 at week 24, the significant predictors were baseline PASI<10 (PASI<10: 0.540 [0.152-0.928], p=0.006) and a lower baseline weight (-0.018 [-0.030- -0.007], p=0.001). Sensitivity analyses for PASI≤3 showed the same predictors.

Sensitivity analyses for the TEs with a low to normal label dose during the first 24 weeks of biologic treatment as well as for the TEs without a treatment interruption, resulted in the same predictors for PASI90 and for PASI≤5 as described previously. Sensitivity analyses for PASI≤3 in low to normal label dose as well as in the TEs without a treatment interruption yielded the same predictors as for PASI≤5.

Additional sensitivity analyses were performed excluding the TEs that used a conventional systemic agent in the first 24 weeks of biologic treatment. These analyses resulted in the same predictor for PASI90, i.e. baseline PASI≥10. Predictors for PASI≤5 were baseline PASI<10, lower baseline BMI (or lower baseline weight) and biologic naivity. Biologic naivity, however, highly correlated with baseline PASI score. Biologic naive patients were significantly more likely to have a baseline PASI≥10 (0.599 [0.214-0.983]; p=0.002) compared with patients that had already used a biologic previously. Baseline BMI or baseline weight did not correlate with baseline PASI score.

Since USTE is dosed by baseline weight (≤100kg or >100kg), baseline weight was divided into these two categories for additional sensitivity analyses. These analyses showed that baseline PASI was the only predictor for PASI90 and PASI≤5 and that baseline weight was not a predictor for PASI≤5 anymore.

Discussion

At week 24 in our real-world prospective cohort of patients with psoriasis treated with biologics, in only a limited number of TEs PASI100 or PASI90 was reached. In all TEs with a PASI100 or PASI90 response, PASI≤5 was also achieved. However, in a

substantial proportion of TEs without a PASI100 or PASI90 response, PASI≤5 was still achieved (58% and 52% respectively). Of note, from TEs with a baseline PASI≥10, a higher proportion achieved PASI≤5 (55%) compared with PASI90 (19%) at week 24. Baseline PASI≥10 was a strong predictor for reaching PASI90 at week 24. Baseline PASI<10 and a lower baseline BMI were predictors for PASI≤5 at week 24.

The prescription of concomitant conventional systemic agents and adjusting dosages of biologics as well as treatment interruptions were allowed in this daily practice cohort to personalize treatment. When analyzing the TEs that were characterized by a low to normal biologic dose compared with EMA label dose during the first 24 weeks of treatment, the same predictors for PASI90 and PASI≤5 were found. This was also the case when analyzing TEs without treatment interruptions, as well as in the TEs in which no conventional systemic agents were used. Sensitivity analyses for weight instead of BMI showed the same predictors for PASI90 and PASI≤5 at week 24. Since the number of TEs for USTE and IFX were small, sensitivity analyses were performed for ADA/ETA as one group. This also resulted in the same predictors for PASI90 and PASI≤5. Our results on the predictors of PASI90 and PASI≤5 therefore seem to be robust.

In our study, PASI≤5 was chosen because PASI≤5 is a goal that is widely accepted amongst physicians and is associated with a good quality of life.[1,4,5] Sensitivity analyses were performed for PASI≤3, since in all TEs in which PASI90 was achieved at week 24, PASI≤3 was also achieved at week 24. These sensitivity analyses showed the same predictors as the analyses for PASI≤5 at week 24, which underscores the robustness of our results.

The opinion about treatment success is changing, with PASI90 becoming the new treatment goal.[1,16] Treatment success, however, can also be defined by reaching PASI100 or PASI≤5. With this study we have shown that in daily practice, patients with psoriasis treated with biologics (ADA, ETA, IFX, USTE) rarely achieved PASI100 (3.3%) or PASI90 (15%) and more frequently achieved PASI≤5 (59%) and even lower absolute PASI scores, such as PASI≤2 (24.2%) at week 24. In RCTs of these biologics, however, PASI90 is often achieved (20-58% of patients) at week 16-28.[21-24] This might be due to the higher PASI score at start of treatment in RCTs compared with daily practice. In our study, high baseline PASI score (PASI≥10) was indeed a predictor for reaching PASI90 at week 24. In addition, in daily practice, patients with psoriasis that switch from one biologic treatment to another could have a lower baseline PASI score than biologic naïve patients. Indeed, we showed that biologic naïve patients had significantly more often a baseline PASI score ≥10 compared with biologic non-naïve patients. Also, the median baseline PASI score in our cohort was 12.8. The mean baseline PASI scores in RCTs were, however, higher and ranged from 18 to 23.[21-24] We also demonstrated that, in daily practice, PASI≤5 was more often achieved than PASI90 or PASI100 at week 24, even in patients with a baseline PASI≥10.

Therefore, PASI90 might not be the most suitable outcome to assess psoriasis severity in patients with psoriasis that are being treated with biologics in daily practice. Based on our results, we advise physicians to monitor absolute PASI scores in daily practice. We also advise to display absolute PASI scores in publications about efficacy/effectiveness from RCTs and cohort studies.

So far, few studies have tried to assess which baseline patient characteristics were associated with the effectiveness of biologics. In literature baseline BMI, baseline severity score (PASI and physician global assessment), duration of psoriasis and biologic naivity are postulated.[6-9] Our study showed that baseline PASI was the most important predictor for PASI90 and one of the important predictors for PASI≤5 at week 24. A lower baseline BMI was an important predictor of treatment response (PASI≤5) at week 24. Both predictors were also found for the more stringent PASI≤3 at week 24. Recently conducted RCTs have shown that weight loss during biologic treatment (ADA, ETA, IFX, USTE) increases the efficacy, also in biologics that are not dosed according to weight.[25,26] Baseline BMI also predicted biologic discontinuation in drug survival studies.[27-31] These findings are important because most biologics are not dosed based on weight and none of the biologics are currently being dosed based on BMI. Patients and physicians might benefit from the finding that baseline BMI is a factor that influences the response to biologic therapy, also because BMI can be influenced by losing weight. More studies are needed to investigate whether weight loss has indeed a positive influence on the short- and long-term efficacy as well as on drug survival of biologic therapies before advising all our patients weight reduction programs.

Limitations of this study are the low patient numbers that achieve PASI90 or PASI100 in daily practice and consequently the inability to perform subanalyses for every biologic agent separately. Our findings warrant replication in larger daily practice studies. A strength of our study is the use of data from the daily practice and multicenter BioCAPTURE registry that results in a high external validity. Other strengths include the registration of biologic doses and concomitant conventional systemic therapies as well as the performed sensitivity analyses.

To conclude, in daily practice where baseline PASI is often lower than in RCTs, a limited number of patients reached PASI100 or PASI90 at 24 weeks of biologic treatment. Inclusion of an absolute PASI score is important in the assessment of psoriasis severity. Our results also underscore the importance of the modifiable predictor baseline BMI for reaching a high response on biologic treatment. Future research into the influence of weight reduction in patients with psoriasis and the influence of BMI on treatment response with newly developed biologics is needed. Furthermore, pharmaceutical companies that perform future studies on biologics are advised to take into account the patients with high baseline BMI when establishing the most appropriate biologic dose.

Supplemental material

Supplement_Table 1 Variables selected as possible predictors from univariate generalized estimating equation regression analyses

Baseline characteristics	*PASI90*	*PASI≤5*
Age at start of biologic	-0.008 [-0.027-0.011]	-0.009 [-0.024-0.006]
Gender (female)	**0.587 [0.013-1.162]**	0.252 [-0.150-0.653]
Weight	-0.007 [-0.024-0.010]	**-0.019 [-0.031- -0.007]**
BMI	-0.031 [-0.083-0.020]	**-0.069 [-0.109- -0.030]**
Family history of psoriasis (no)	**0.543 [-0.090-1.175]**	0.150 [-0.266-0.566]
Diagnosis of PSA (no)	0.012 [-0.547-0.571]	-0.057 [-0.476-0.362]
Duration of psoriasis	-0.002 [-0.023-0.019]	-0.003 [-0.019-0.013]
Baseline PASI (PASI<10)§	**1.284 [0.541-2.027]**	**-0.581 [-0.969- -0.194]**
Biologic naïve (no)	0.309 [-0.204-0.822]	**0.280 [-0.097-0.657]**

Numbers are presented as regression coefficient (B) [95% confidence intervals]. Bold regression coefficients had a P-value of <0.2 and were incorporated into the multivariate generalized estimating equation regression analysis as described in the method section.
§ PASI: psoriasis area and severity index; divided into PASI≥10 and PASI<10

Supplement_Table 2 Treatment characteristics of included treatment episodes (TEs)

Biologic dose during first 24 weeks	***Adalimumab N= 159 TEs***	***Etanercept N= 193 TEs***	***Infliximab N= 19 TEs***	***Ustekinumab N= 83 TEs***
Biologic dose (mg)	596 ± 112	1895 ± 425	2344 ± 385	169 ± 60
Biologic dose per interval (induction dose included)	46 [0] mg per 2 weeks	72 [17] mg per week	7.6 [0] mg/kg/8 weeks	62 [21] mg per 12 weeks
Total dose higher than expected by EMA label (yes)	28 (17.6%)	87 (45.1%)	0 (0%)	9 (10.8%)
Conventional systemic agent during first 24 weeks	***Adalimumab N= 159 TEs***	***Etanercept N= 193 TEs***	***Infliximab N= 19 TEs***	***Ustekinumab N= 83 TEs***
Conventional systemic agent during TE (yes)	41 (25.8%)	48 (24.9%)	9 (47.4%)	16 (19.3%)
Conventional systemic agents (number of agents)	Total: 42 MTX: 32 (76%) CyA: 7 (17%) NT: 3 (7%) FAE: 0 (0%)	Total: 48 MTX: 31 (65%) CyA: 8 (17%) NT: 5 (10%) FAE: 4 (8%)	Total: 9 MTX: 8 (89%) CyA: 0 (0%) NT: 1 (11%) FAE: 0 (0%)	Total: 16 MTX: 11 (69%) CyA: 1 (6%) NT: 4 (25%) FAE: 0 (0%)

Mean ± SD, Median [IQR], N(%). EMA: European Medicines Agency. MTX: methotrexate; CyA: cyclosporine; NT: acitretin; FAE: fumaric acid esters.

References

1 Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2015; 29: 645-8.

2 Torii H, Sato N, Yoshinari T et al. Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: an analysis of Japanese clinical trials of infliximab. The Journal of dermatology 2012; 39: 253-9.

3 Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 333-7.

4 Reich K, Nestle FO, Papp K et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. The British journal of dermatology 2006; 154: 1161-8.

5 Reich K, Griffiths CE. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. Archives of dermatological research 2008; 300: 537-44.

6 Strober BE, Bissonnette R, Fiorentino D et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). Journal of the American Academy of Dermatology 2016.

7 Menting SP, Sitaram AS, Bonnerjee-van der Stok HM et al. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. The British journal of dermatology 2014; 171: 875-83.

8 van Lumig PP, van de Kerkhof PC, Boezeman JB et al. Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naive vs. non-naive patients. Journal of the European Academy of Dermatology and Venereology : JEADV 2013; 27: 593-600.

9 Shear NH, Hartmann M, Toledo-Bahena M et al. Long-term efficacy and safety of infliximab maintenance therapy in patients with plaque-type psoriasis in real-world practice. The British journal of dermatology 2014; 171: 631-41.

10 Zweegers J, van den Reek JM, van de Kerkhof PC et al. Comparing treatment goals for psoriasis with treatment decisions in daily practice: results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE. The British journal of dermatology 2014; 171: 1091-8.

11 Zweegers J, de Jong EM, Nijsten TE et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatology online journal 2014; 20.

12 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV 2009; 23 Suppl 2: 1-70.

13 Warren RB, Smith CH, Yiu ZZ et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). The Journal of investigative dermatology 2015; 135: 2632-40.

14 van den Reek JM, Zweegers J, Kievit W et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. The British journal of dermatology 2014; 171: 1189-96.

15 Esposito M, Gisondi P, Cassano N et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. The British journal of dermatology 2013; 169: 666-72.

16 Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Archives of dermatological research 2011; 303: 1-10.

17 Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 2: 12-20.

18 Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988; 44: 1049-60.
19 Menter A, Thaci D, Papp KA et al. Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. Journal of the American Academy of Dermatology 2015; 73: 410-9 e6.
20 Hagg D, Eriksson M, Sundstrom A et al. The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. PloS one 2013; 8: e63619.
21 Leonardi CL, Powers JL, Matheson RT et al. Etanercept as monotherapy in patients with psoriasis. The New England journal of medicine 2003; 349: 2014-22.
22 Menter A, Tyring SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. Journal of the American Academy of Dermatology 2008; 58: 106-15.
23 Reich K, Nestle FO, Papp K et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005; 366: 1367-74.
24 Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1665-74.
25 Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert opinion on biological therapy 2014; 14: 749-56.
26 Naldi L, Conti A, Cazzaniga S et al. Diet and physical exercise in psoriasis: a randomized controlled trial. The British journal of dermatology 2014; 170: 634-42.
27 Zweegers J, van den Reek JM, van de Kerkhof PC et al. Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in psoriasis patients treated with adalimumab, etanercept or ustekinumab in daily practice. A prospective, comparative, long-term drug survival study from the BioCAPTURE registry. The British journal of dermatology 2016.
28 Puig L, Ruiz-Salas V. Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis. Dermatology 2015; 230: 46-54.
29 Spertino J, Lopez-Ferrer A, Vilarrasa E et al. Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 1514-21.
30 van den Reek JM, van Lumig PP, Driessen RJ et al. Determinants of drug survival for etanercept in a long-term daily practice cohort of patients with psoriasis. The British journal of dermatology 2014; 170: 415-24.
31 Carrascosa JM, Vilavella M, Garcia-Doval I et al. Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 907-14.

PART III

DRUG SURVIVAL

8

‘Happy’ drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: *results from the BioCAPTURE network*

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Abstract

Background: Drug survival is a marker for treatment success. To date, no analyses relating dermatological quality-of-life measures to drug survival have been published.
Objectives: (i) To describe 1-year drug survival for adalimumab, etanercept, and ustekinumab in a daily practice psoriasis cohort, and (ii) to introduce the concept of 'happy' drug survival, defined as Dermatology Life Quality Index (DLQI) ≤ 5 combined with being 'on-drug' at a specific time point.
Methods: Data were extracted from a prospective registry. Drug survival was analysed using Kaplan-Meier estimates. 'Happy' drug survival was calculated, with data split into 'happy' (DLQI ≤ 5) vs. 'unhappy' (DLQI > 5) at baseline and month 3, 6, 9, and 12.
Results: 249 treatment episodes were included (101 adalimumab, 82 etanercept, 66 ustekinumab). The 1-year drug survival rates for ustekinumab, adalimumab, and etanercept were 85%, 74%, and 68%, respectively. Ustekinumab showed a better confounder-corrected drug survival vs. etanercept (Hazard Ratio (HR) 3.8, $p = 0.02$) and a trend towards better survival vs. adalimumab (HR 2.3, $p = 0.1$). At baseline, the majority (n=115, 73%) was considered 'unhappy' and a minority 'happy' (n=42, 27%) (ratio 'happy':'unhappy' was 1 : 2.7). The percentage of treatment episodes with 'happy' on-drug patients increased to 79% after 1 year.
Conclusions: Ustekinumab showed a better overall drug survival than etanercept, and a trend towards a better overall drug survival than adalimumab. After 1 year, patients reported to be 'happy' in 79% of episodes and 'unhappy' in 21%. We introduced the new concept of 'happy' drug survival because the proportion of on-drug patients with good quality of life is an important indicator for treatment success.

Introduction

In daily practice, adalimumab (ADA), etanercept (ETA) and ustekinumab (USTE) are frequently used biologics for the treatment of moderate-to-severe psoriasis when patients do not respond, or have a contraindication to, classic antipsoriatic treatments. In January 2009, USTE was registered; from that time point on, all three agents were equally available. ETA and ADA share their target, as both agents inhibit tumour necrosis factor (TNF)-α.[1] In contrast, USTE inhibits interleukins 12 and 23 by binding to the shared p40 unit.[2] All three agents have shown their efficacy and safety in multiple (randomized) controlled trials.[3-18] Real-world drug survival studies comprising survival rates and associated predictors of ADA and ETA have been published, but vary in study design and outcome.[19-23] Studies regarding drug survival of USTE are scarce.[24,25] Clemmensen *et al.* found that only 4.5% of patients discontinued USTE after 321 days. Lack of response to previous anti-TNF-α treatment did not impair the response to USTE.[24] In a retrospective Japanese psoriasis cohort, the 1-year drug survival of USTE was 97%.[25]

In addition to the above-mentioned drug survival studies, quality-of-life (QoL) measures are also important in the process of evaluating psoriasis treatments. For this purpose, we introduced a new concept named 'happy' drug survival, combining drug survival rates with QoL. We used the Dermatology Life Quality Index (DLQI), a frequently used QoL measure in dermatological research.[26,27] A DLQI < 5 is considered to reflect no or mild influence on QoL.[28] In this study, we explored the proportion of 'on-drug' patients who also achieved a good dermatological QoL, as defined by DQLI ≤ 5.

The objectives of this study were (i) to describe the 1-year drug survival for ADA, ETA and USTE in a daily practice psoriasis cohort during a period when all agents were equally available; and (ii) to analyse the proportion of treatment episodes in which patients showed a 'happy' drug survival in the first year of treatment (DLQI ≤ 5 and being 'on-drug').

Methods

BioCAPTURE registry

Dermatology Life Quality Index measures and data on drug survival were extracted from a prospective registry containing daily practice data from all patients with psoriasis treated with biologics (BioCAPTURE, Continuous Assessment of Psoriasis Treatment Use REgistry with biologics). This registry was founded at the department of Dermatology of the Radboud University Medical Center Nijmegen in 2005 and is based there. Eight regional nonacademic centres have participated in the registry

since 2011. The BioCAPTURE registry was approved by the medical ethics committee of the Radboud University Medical Center. According to Dutch law, informed consent from patients was not mandatory in this noninterventional study, but it is currently obtained from every newly included patient.

Protocol and data collection

Preferably, patients were treated according to the regimens recommended by the European Medicines Agency label and the European and Dutch national guidelines for treatment with biologics.[29,30] Patients started one of the following treatments: (i) ADA induction dose of 80 mg at start and 40 mg at week 1, followed by a maintenance dose of 40 mg every other week; (ii) ETA 50 mg twice weekly for the first 12 weeks, followed by 50 mg weekly; or (iii) USTE 45 mg (body weight $<$ 100kg) or 90 mg (body weight $\geq$ 100kg) at baseline, then after 4 weeks and every 12 weeks thereafter. Dosage adjustments, interval changes and/or combination therapy with topical or conventional antipsoriatic systemic therapies were allowed as this study reflects daily practice. When the biologic was considered ineffective by the treating physician and/or was considered to be related to severe or disturbing side effects, it was withdrawn. Patients were seen approximately once every 3 months at our outpatient department and data were collected at every visit. Collected data included patient and treatment characteristics, effectiveness [including Psoriasis Area and Severity Index (PASI)], side effects and medication adjustments. Every 3 months, patients received questionnaires (including DLQI) by mail. All data were entered into a Microsoft Access database and checked for completeness by the data manager. For further statistical analyses, data were analysed with SPSS Statistics 20.0 (IBM, Armonk, NY, U.S.A.).

Drug survival analysis

ADA, ETA and USTE treatment episodes starting from January 2010 were analysed in this study. Infliximab was left out of the analysis due to a low number of patients. If patients received more than one treatment episode of the same agent (e.g. two episodes of ETA) in our registry, only the first treatment episode was analysed. If patients received different agents in our registry, all treatment episodes were analysed. The follow-up period was $\geq$ 6 months. When a treatment episode was interrupted for $<$ 90 days, it was considered as one continuous episode. Patients often discontinue their treatment for short intervals due to holidays, infections or (elective) surgery. In recently published drug survival studies, 90 days was an accepted maximum interruption period.[20,31]

We analysed drug survival rates using Kaplan-Meier estimates. Every discontinuation was considered as an event in the survival analysis. Patients were censored when lost to follow-up, or if still using the biologic at the moment of data lock. Drug survival rates were read from the Kaplan-Meier survival curves. Differences in drug survival

between groups were analysed using a log-rank (Mantel-Cox) test, or described when survival curves crossed.
A sensitivity analysis for USTE drug survival was carried out to take account of the different discontinuation dates that can be chosen when analyzing this agent. In this manuscript, we present the last date of injection plus 8, 10 or 12 weeks (depending on the original scheme of the patient) in our primary analyses (most positive approach). In contrast with this approach, the last date of injection can be chosen as the USTE discontinuation date (most conservative approach). This sensitivity analysis is presented separately.
For all biologics taken together, the difference between overall drug survival curves was compared for biologic naive versus non-naive episodes.

Confounder correction of drug survival analysis

Patient and treatment characteristics were compared for ADA, ETA, and USTE treatment episodes, and for biologic naive and non-naive episodes. Pearson's chi-squared test was used for characteristics with categorical outcomes. For the comparison of characteristics between the three different agents, a one-way ANOVA for continuous outcomes with a parametric distribution, and a Kruskal-Wallis test for continuous outcomes with a nonparametric distribution was used. For the comparison based on biologic naive versus non-naive episodes, characteristics with continuous outcomes with a parametric distribution were analysed using an independent t-test or, in case of a nonparametric distribution, using a Mann-Whitney U test. When characteristics were significantly different between groups they were corrected for using multivariate Cox regression analysis. If closely related variables were both candidates for confounder correction (e.g. weight and body mass index), a selection based on biological mechanisms was made to choose only one confounder. Sex and age were included as fixed variables in all models independent of their significance value. Subsequently, possible confounders were added as covariates to this model. Hazard ratios with P-values resulting from this multivariate Cox regression analysis are described.

'Happy' drug survival

'Happy' drug survival was defined as DLQI ≤ 5 and being 'on-drug' at a specific time point. A DLQI > 5 while being 'on-drug' was considered as an 'unhappy' treatment episode. All patients who returned at least one DLQI questionnaire in the first year of treatment were included in this analysis. Ratios and percentages for 'happy' vs. 'unhappy' episodes were calculated at 0, 3, 6, 9, and 12 months using a per protocol approach. Missing data were found to be at random time points and were handled as such. To synchronize the drug survival curve with the DLQI measurement points, an actuarial drug survival analysis was carried out. The actuarial survival curve and the

frequencies of DLQI ≤ 5 ('happy') and DLQI > 5 ('unhappy') were visualized in one graph. Not all patients returned questionnaires; therefore this subanalysis consisted of a smaller group than the original cohort in this paper. A head-to-head comparison of 'happy' drug survival curves between the different treatments was considered inappropriate due to lack of power.

Results

Patient and treatment characteristics

In total of 249 treatment episodes in 213 unique patients were included in this drug survival analysis, comprising 101 ADA episodes, 82 ETA episodes and 66 USTE episodes. Patient and treatment characteristics for each drug are presented in Tables 1 and 2. For all agents taken together, 59 episodes (24%) were discontinued in the first year. The most frequent reason for discontinuation was ineffectiveness of therapy (n=33, 13%), followed by side effects (n=16, 6%), and a combination of ineffectiveness and side effects (n=7, 3%). Three treatments were stopped due to other reasons (wish for pregnancy, ineffectiveness of biologic on arthritis symptoms, and work-related issues). The median dosage of ADA was 40mg every 2 weeks, and the

Table 1 Patient characteristics

	ADA N=101	**ETA** N= 82	**USTE** N= 66	**P-value**
Sex (male)	59 (58.4)	47 (57.3)	40 (60.6)	0.91[g]
Age (years)[a]	46.4 ± 12.2	46.1 ± 14.2	48.9 ± 12.5	0.35[h]
Age at onset of psoriasis (years)	22.2 [0-57.8]	19.8 [0-58.1]	25.8 [2.3-66.5]	0.07[f]
Disease duration (years)	20.8 [0.9-53.6]	19.3 [0.5-63.9]	17.1 [2.9-57.2]	0.55[f]
Psoriatic arthritis (yes)	29 (35.4)[c]	18 (27.3)[d]	16 (31.4)[e]	0.48[g]
Weight (kg)	89.8 ± 18.8	82.5 ± 17.8	93.0 ± 17.3	*0.01*[h]
BMI (kg m^{-2})	28.8 ± 5.6	26.8 [17.7-55.1]	29.4 [21.9-59.0]	*0.02*[f]
Baseline PASI[b]	11.3 [2.6-38.4]	11.8 [0.6-42.1]	15.4 ± 7.8	*0.03*[f]
Treated at an academic center	73 (72.3)	59 (72.0)	39 (59.1)	0.15[g]
Treated at a nonacademic center	28 (27.7)	23 (28.0)	27 (40.9)	

mean±SD, median [range], n (%)

ADA: adalimumab; ETA: etanercept; USTE: ustekinumab; PASI: Psoriasis Area and Severity Index. [a] Age at time of inclusion in this study, [b]90 days before, or 7 days after starting the study biologic. Psoriatic arthritis status for [c]82, [d]66, [e]51 patients available. [f]Kruskal-Wallis test, [g]Pearson's chi-squared test, [h]One way ANOVA

Table 2 Treatment characteristics

	ADA N=101	ETA N=82	USTE N=66	P-value
Naive for biologics Naive for TNF-α antagonists	49 (48.5) 51 (50.5)	53 (64.6) 54 (65.9)	21 (31.8) 25 (37.9)	*< 0.001*[f] *< 0.001*[f]
Median dose Median dose (pt <100kg) Median dose (pt ≥100kg)	40.0 [26.7-93.3][a] NA NA	75.3 [50.0-100.0][b] NA NA	45.0 [35.8-135.0][c] 45.0 [35.8-113.5][d] 68.3 [45.0-108.0][e]	NA
Concomitant methotrexate Concomitant acitretin	27 (26.7) 1 (1.0)	16 (19.5) 4 (4.9)	10 (15.2) 2 (3.0)	0.18[f] NA[g]
Reason for discontinuation: Ineffectiveness Side effects Ineffectiveness and side effects Other reasons Lost to follow up	 15 (14.9) 5 (5.0) 5 (5.0) 1 (1.0) 1 (1.0)	 14 (17.1) 8 (9.8) 2 (2.4) 0 (0.0) 2 (2.4)	 4 (6.1) 3 (4.5) 0 (0.0) 2 (3.0) 2 (3.0)	 NA

mean±SD, median [range], n (%)

ADA, adalimumab; ETA, etanercept; USTE, ustekinumab; TNF, tumour necrosis factor; NA, not applicable. Data from [a]101, [b]75, [c]63, [d]34, [e]16 available. [f]Pearson's chi-squared test, [g]Pearson's chi-squared test not possible due to insufficient cases with acitretin.

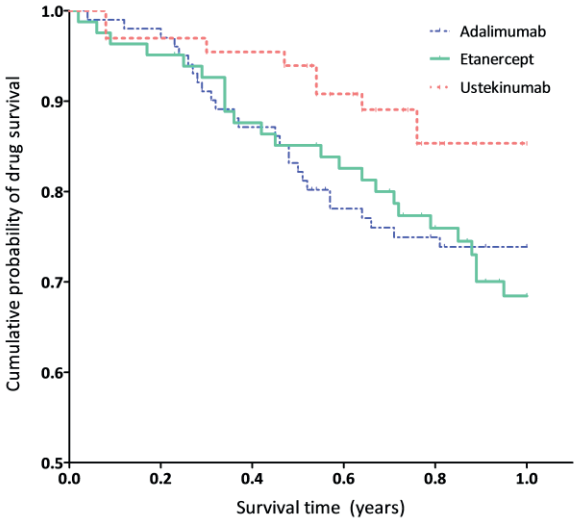
median dosage of ETA was 75mg per week. For USTE, the median dosage was 45mg per 12 weeks in patients weighing
< 100kg and 68mg per 12 weeks in patients weighing ≥ 100kg. Thus the median ETA dose was higher, and the median USTE dose in patients weighing ≥ 100kg was lower than the recommended label dose. Other median dosages corresponded with the recommended dose. All characteristics were compared for differences between drugs. Characteristics that were statistically different between drugs were incorporated in the confounder-corrected subanalysis as described later.

Drug survival rates

In the uncorrected survival curves, the highest absolute 1-year survival rates were seen for USTE followed by ADA and ETA, with percentages of 85%, 74% and 68%, respectively (Fig. 1). The drug survival of USTE was significantly higher than that of ETA (log-rank test, $p= 0.032$), and USTE showed a trend towards a better survival than ADA (log-rank test, $p= 0.066$). The curves for ADA and ETA drug survival crossed over frequently, therefore no statistical analysis was carried out to compare these two biologics. Sensitivity analysis of overall drug survival, with conservative

handling of USTE discontinuation dates (date of discontinuation was date of last injection), also revealed a better of drug survival of USTE vs. ETA, and a trend towards a better survival vs. ADA (log-rank test, $p = 0.039$ and $p = 0.085$, respectively).

Figure 1 Overall 1-year drug survival of adalimumab, etanercept and ustekinumab for patients with psoriasis



N=249, event=discontinuation in general. In all groups, no median drug survival could be calculated as > 50% of patients were still on-drug at the end of the study. In the first 3 months of treatment, survival curves for the different agents cross; after 3 months, a trend towards a better drug survival for ustekinumab was seen.

Drug survival rates with confounder correction

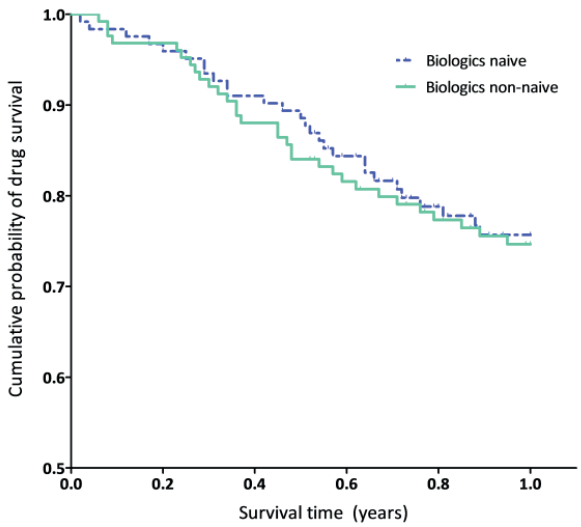
The baseline variables weight, PASI and prior biologics were significantly different when compared between the three agents (Tables 1 and 2). These variables were therefore included for confounder correction, together with the fixed variables age and sex. For confounder-corrected overall drug survival, USTE drug survival was higher than that of ETA (Hazard Ratio (HR) 3.822; 95% confidence interval (95% CI) 1.203-12.139; $p = 0.023$), and showed a trend towards a better survival than that of ADA (HR 2.330; 95% CI 0.837-6.489; $p = 0.1$). ETA and ADA showed similar drug survival curves (HR 1.132, 95% CI 0.565-2.269, $p = 0.727$).

As for the confounder-corrected sensitivity analysis with conservative handling of USTE discontinuation dates, USTE drug survival was still significantly higher than that of ETA (HR 3.604, 95% CI 1.135-11.443, *p= 0.03*), and showed a trend towards a better survival than that of ADA (HR 2.147, 95% CI 0.769-5.991, *p= 0.14*).

Drug survival rates for biologic naive vs. non-naive episodes

For ADA, ETA and USTE taken together, Kaplan-Meier curves did not show different trends for biologic naive vs. non-naive treatment episodes (log-rank test, *p= 0.803*) (Fig. 2). About half (49%, n=123) of the treatment episodes considered biologic naive treatments and 51% (n=126) biologic non-naive. The absolute 1-year drug survival percentages were 76% in biologic naive and 75% in non-naive treatments. Survival curves were corrected for the following possible confounders: treatment setting, drug, disease duration and baseline PASI, together with age and sex as fixed variables. No statistically significant difference between biologic naive and non-naive treatment episodes was seen after confounder correction (HR 0.99, 95% CI 0.536-1.814, *p 0.965*).

Figure 2 Overall 1-year drug survival of biologic naive vs. non-naive patients with psoriasis

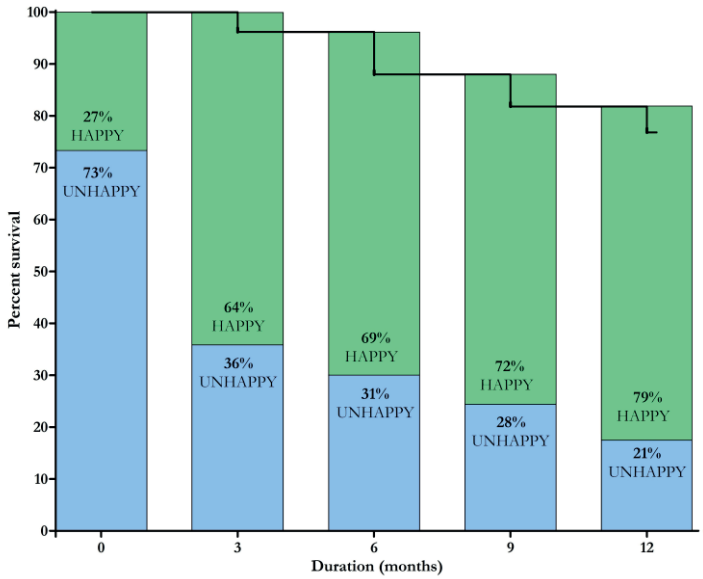


N=249, event=discontinuation in general. In both groups, no median drug survival time could be calculated as > 50% of patients were still on-drug at the end of study. After 1 year, no trends towards a difference between the overall drug survival for naive vs. non-naive patients is seen.

‘Happy’ drug survival

Figure 3 shows the ‘happy’ drug survival curve. This subcohort consisted of 74 ADA (40%), 62 ETA (33%), and 50 USTE (27%) episodes in which at least one DLQI questionnaire was returned in the first year of treatment. The subcohort accounted for 75% of the original cohort. At baseline, the majority of patients who returned the questionnaire at start of the study (157 of 186) were considered ‘unhappy’ (n=115, 73%), with a DLQI score > 5. A minority were considered ‘happy’ (n=42, 27%). The ratio of ‘happy’ to ‘unhappy’ was 1 : 2.7 at that time. Of all returned questionnaires, the relative percentage considered ‘happy’ increased over time. In 64%, 69%, 72%, 79% of the episodes a DQLI ≤ 5 was scored after 3, 6, 9 and 12 months, respectively. This led to reversed ‘happy’ : ‘unhappy’ ratios compared with the baseline ratio. Ratios of 1.8 : 1, 2.2 : 1, 2.6 : 1, and 3.7 : 1 were seen after 3, 6, 9 and 12 months, respectively.

Figure 3 ‘Happy’ drug survival of patients with psoriasis on adalimumab, etanercept or ustekinumab



‘Happy’ drug survival combines the actuarial drug survival of biologics (black line) with the percentage of patients with Dermatology Life Quality Index (DLQI) ≤ 5 (‘happy’) vs. DLQI > 5 (‘unhappy’). This cohort consisted of 186 treatment episodes: 74 with adalimumab, 62 with etanercept and 50 with ustekinumab. Data were available for only 157 patients at baseline.

Analysis comparing the group that returned DLQI questionnaires revealed no differences in baseline characteristics compared with the group in which no questionnaires were returned, except for the fact that the responder group was larger in nonacademic hospitals (Pearson's chi-squared test, $p = 0.02$). At baseline and months 3, 6, 9, and 12, questionnaires were not returned in 16%, 34%, 40%, 42%, and 40% of cases, respectively.

Discussion

The 1-year drug survival rates of USTE, ADA and ETA were 85%, 74% and 68% respectively. Multivariate Cox regression analysis of drug survival corrected for confounders showed that USTE had a significantly better 1-year drug survival rate than ETA, and had a trend towards a better drug survival than ADA. Biologic naive and non-naive treatment episodes had comparable 1-year drug survival rates. The proportion of on-drug patients with a good QoL is an important indication of treatment success. For this purpose, we introduced the 'happy' drug survival analysis. At the moment of initiating a biologic in the majority of episodes patients reported to be 'unhappy' (DLQI $>$ 5), with a ratio of 1.0 : 2.7 for 'happy' vs. 'unhappy'. In time, this ratio reversed, leading to a majority of 'happy' (DLQI $\leq$ 5) on-drug episodes, with a ratio of 3.7 : 1.0 after 12 months.

Clemmensen et al. have shown a better USTE drug survival than ADA and ETA together.[24] We found a 1-year drug survival rate of 85% for USTE, which was slightly lower than survival rates in the Danish cohort[24] and in a retrospective Japanese cohort.[25] In these studies, USTE 1-year survival rates of
$>$ 90% were found. We found no differences in drug survival rates for biologic naive vs. non-naive patients. These results correspond with many previous studies on drug survival and efficacy [23,32-39], but contradict Danish studies on drug survival.[21,24] Dosages of biologics could influence drug survival. In the present cohort, the median doses of ADA, and USTE patients $<$ 100kg, corresponded with the dose recommended by the label. However, USTE patients $\geq$ 100kg used a slightly lower dose than the recommended dose, and patients on ETA used a higher dose. From this study design, we cannot evaluate whether lower ETA dosages would lead to different survival curves. The influence of underdosing in USTE is thought to be of limited influence, as doctors were free to increase the dose in case of nonresponse. Another hypothesis regarding influencing factors of drug survival is that the low frequency of USTE injections could lead to better compliance and therefore better drug survival. We were however not able to test this in the present study.

The new concept of 'happy' drug survival was used to investigate whether drug survival corresponds with a good dermatological QoL. This concept provides a

broader measurement of treatment success, combining drug survival with patient-reported outcomes. As DLQI is a frequently used QoI tool in daily practice and in clinical studies, the present concept is thought to be easily adaptable to various settings. Eventually, this broad measurement could be used in large groups to compare different biologics. In the present cohort, we found a pronounced increase in the proportion of treatment episodes with 'happy' patients using biologics after 3 months, followed by a gradual rise until 12 months. After 1 year, most episodes with on-drug patients showed a good disease-related QoL. Still, one-fifth of this treated group reported a DLQI > 5. It is important to identify the needs that are not fulfilled for this subgroup.

It must be taken into account that this drug survival study is based on a daily practice, whereby different factors could be of influence. Important factors are the behaviour of physicians and patients and the availability of other treatment options. To minimize the influence of these factors, both academic and peripheral patients and doctors were represented, and data were collected in a time frame in which ADA, ETA and USTE were equally available. As the groups (ADA, ETA, USTE) were heterogeneous for specific characteristics, we corrected for possible confounders using a multivariate Cox regression model. For instance, we corrected for biologic naivety because more biologic non-naive patients were present in the USTE group. This could hypothetically lead to a longer persistence due to a limited number of alternatives. The corrected survival curves still show the same results as the uncorrected version, and we therefore think that the influence of non-naivety is limited. Moreover, in the vast majority of cases infliximab was still available, and in many cases one of the other anti-TNF-α agents as well.

Patients were not randomized to treatments and this could have led to selection bias. However, this bias is inherent in a noninterventional daily practice study. As this study is based on daily practice research, dose adjustments and use of antipsoriatic comedication was allowed. Methotrexate use was substantial, but we found no difference in the amount of users between drugs. Therefore, it was not considered to be a confounder. To evaluate whether drug survival of a specific biologic could be improved by addition of methotrexate, a randomized study would be preferred.

The 'happy' drug survival analysis is based partly on questionnaires, wherein responder bias could have played a role. Missing questionnaires were at random time points, therefore no selection bias for questionnaires at specific time points was expected in this study. The DLQI is designed to measure disease-related QoL, hence the term 'happy' in the 'happy' drug survival concept refers to cutaneous disease-related QoL. However, it is plausible that major life events or non-disease related issues could have influenced the 'happy' drug survival.

This study shows that ADA, ETA and USTE have high real-world drug survival rates in the first year of therapy. USTE showed a better overall drug survival than ETA and a

trend towards a better drug survival than ADA. Treatment episodes with and without prior biologics showed no differences in drug survival rates, which is reassuring within the context of switching to other therapies.
We introduced the 'happy' drug survival analysis as a new concept combining QoL measures with drug survival. The proportion of episodes with 'happy' on-drug patients increased from 27% at baseline to 79% after 12 months. It is important to identify the needs that are not fulfilled for the subgroup of 'unhappy' patients. Measuring whether actively treated patients have a good disease-related QoL is an indicator for treatment success. The concept of 'happy' drug survival could be a meaningful tool to bring patient care to a next level.

References

1. Horiuchi T, Mitoma H, Harashima S et al. Transmembrane TNF-alpha: structure, function and interaction with anti-TNF agents. Rheumatology 2010; 49: 1215-28.
2. Benson JM, Sachs CW, Treacy G et al. Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. Nature biotechnology 2011; 29: 615-24.
3. Leonardi C, Strober B, Gottlieb AB et al. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. Journal of drugs in dermatology : JDD 2010; 9: 928-37.
4. Moore A, Gordon KB, Kang S et al. A randomised, open-label trial of continuous vs. interrupted etanercept therapy in the treatment of psoriasis. Journal of the American Academy of Dermatology 2007; 56: 598-603.
5. Schmitt J, Rosumeck S, Thomaschewski G et al. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomised controlled trials. The British journal of dermatology 2013.
6. Tyring S, Gordon KB, Poulin Y et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Archives of dermatology 2007; 143: 719-26.
7. van de Kerkhof PC, Segaert S, Lahfa M et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomised controlled trial with open-label extension. The British journal of dermatology 2008; 159: 1177-85.
8. Kimball AB, Papp KA, Wasfi Y et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. Journal of the European Academy of Dermatology and Venereology : JEADV 2012.
9. Tsai TF, Ho JC, Song M et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomised, placebo-controlled trial in Taiwanese and Korean patients (PEARL). Journal of dermatological science 2011; 63: 154-63.
10. Kumar N, Narang K, Cressey BD et al. Long-term safety of ustekinumab for psoriasis. Expert opinion on drug safety 2013; 12: 757-65.
11. Papp KA, Griffiths CE, Gordon K et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. The British journal of dermatology 2013; 168: 844-54.
12. Puig L, Lopez A, Vilarrasa E et al. Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomised controlled trials with different time points. Journal of the European Academy of Dermatology and Venereology : JEADV 2013.
13. Pariser DM, Leonardi CL, Gordon K et al. Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. Journal of the American Academy of Dermatology 2012; 67: 245-56.
14. Igarashi A, Kato T, Kato M et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. The Journal of dermatology 2012; 39: 242-52.
15. Menter A, Tyring SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: A randomised, controlled phase III trial. Journal of the American Academy of Dermatology 2008; 58: 106-15.
16. Leonardi C, Papp K, Strober B et al. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. American journal of clinical dermatology 2011; 12: 321-37.
17. Gordon KB, Langley RG, Leonardi C et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomised controlled trial and open-label extension study. Journal of the American Academy of Dermatology 2006; 55: 598-606.
18. Asahina A, Nakagawa H, Etoh T et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomised controlled study. The Journal of dermatology 2010; 37: 299-310.
19. Brunasso AM, Puntoni M, Massone C. Drug survival rates of biologic treatments in patients with psoriasis vulgaris. The British journal of dermatology 2012; 166: 447-9.

20. Esposito M, Gisondi P, Cassano N et al. Survival rate of anti-TNF alpha treatments for psoriasis in routine dermatological practice: a multicenter observational study. The British journal of dermatology 2013.
21. Gniadecki R, Kragballe K, Dam TN et al. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. The British journal of dermatology 2011; 164: 1091-6.
22. Lopez-Ferrer A, Vilarrasa E, Gich IJ et al. Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single spanish centre. The British journal of dermatology 2013.
23. van den Reek JM, van Lumig PP, Driessen RJ et al. Determinants of drug-survival of etanercept for psoriasis in a long-term daily practice cohort. The British journal of dermatology 2013.
24. Clemmensen A, Spon M, Skov L et al. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25: 1037-40.
25. Umezawa Y, Nobeyama Y, Hayashi M et al. Drug survival rates in patients with psoriasis after treatment with biologics. The Journal of dermatology 2013.
26. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clinical and experimental dermatology 1994; 19: 210-6.
27. Finlay AY, Basra MK, Piguet V et al. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. The Journal of investigative dermatology 2012; 132: 2464-5.
28. Hongbo Y, Thomas CL, Harrison MA et al. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? The Journal of investigative dermatology 2005; 125: 659-64.
29. Zweegers J, de Jong EM, Nijsten TE et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatol Online J 2014; 20.
30. Nast A, Boehncke WH, Mrowietz U et al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 2012; 10 Suppl 2: S1-95.
31. Glintborg B, Ostergaard M, Dreyer L et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: results from the nationwide Danish DANBIO registry. Arthritis and rheumatism 2011; 63: 382-90.
32. Bissonnette R, Bolduc C, Poulin Y et al. Efficacy and safety of adalimumab in patients with plaque psoriasis who have shown an unsatisfactory response to etanercept. Journal of the American Academy of Dermatology 2010; 63: 228-34.
33. Cassano N, Galluccio A, De Simone C et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. Journal of biologic regulators and homeostatic agents 2008; 22: 233-7.
34. Martyn-Simmons CL, Green L, Ash G et al. Adalimumab for psoriasis patients who are non-responders to etanercept: open-label prospective evaluation. Journal of the European Academy of Dermatology and Venereology : JEADV 2009; 23: 1394-7.
35. Ortonne JP, Chimenti S, Reich K et al. Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25: 1012-20.
36. Papoutsaki M, Chimenti MS, Costanzo A et al. Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. Journal of the American Academy of Dermatology 2007; 57: 269-75.
37. Van L, Modi SV, Yang DJ et al. Sustained efficacy and safety of adalimumab in psoriasis treatment: a retrospective study of 49 patients with and without a history of TNF-alpha antagonist treatment. Archives of dermatology 2008; 144: 804-6.
38. van Lumig PP, van de Kerkhof PC, Boezeman JB et al. Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naive vs. non-naive patients. Journal of the European Academy of Dermatology and Venereology : JEADV 2013; 27: 593-600.
39. Yamauchi PS, Mau N. Adalimumab treats psoriasis in patients previously treated with etanercept: a case series. Journal of the American Academy of Dermatology 2009; 61: 158-60.

9

Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in patients with psoriasis treated with adalimumab, etanercept or ustekinumab in daily practice.

A prospective, comparative, long-term drug survival study from the BioCAPTURE registry

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Abstract

Background: Predictors for successful treatment are important for personalized medicine. Predictors for drug survival of biologics in psoriasis have been assessed but not split for different biologics nor for the reason of discontinuation.

Objectives: To compare long-term drug survival between the outpatient biologics adalimumab, etanercept and ustekinumab in patients with psoriasis and to elucidate predictors for overall survival, drug discontinuation due to ineffectiveness and due to side-effects for every biologic separately.

Methods: Ten years of data were extracted from the prospective, multicenter, long-term BioCAPTURE registry. Kaplan Meyer survival analyses and confounder-corrected Multivariate Cox Regression analysis for Drug Survival (MCR-DS) were performed to compare drug survival between biologics. To elucidate the predictors for different reasons of discontinuation for every biologic, univariate Cox regression analyses and Multivariate Cox Regression analyses for Predictors (MCR-P) with backward selection were performed.

Results: In total, 526 treatment episodes - 186 adalimumab, 238 etanercept and 102 ustekinumab - were included covering 1333 treatment years. MCR-DS showed a significantly higher overall survival for ustekinumab compared with adalimumab and etanercept. MCR-P showed that higher body mass index (BMI) was a predictor for discontinuation due to ineffectiveness for etanercept and ustekinumab and that female sex was a predictor for discontinuation due to side-effects for adalimumab, etanercept and ustekinumab.

Conclusions: Ustekinumab has the highest confounder-corrected long-term drug survival in psoriasis treatment compared with adalimumab and etanercept. Higher BMI is a predictor for discontinuation due to ineffectiveness in etanercept and ustekinumab, and female sex is a consistent predictor for discontinuation due to side-effects in all three outpatient biologics.

Introduction

Adalimumab (ADA), etanercept (ETA) and ustekinumab (USTE) have enriched the therapeutic armamentarium of dermatologists by increasing the number of drugs available for outpatient psoriasis treatment.[1] In order to optimize psoriasis treatment strategies in clinical practice, several real-world studies have assessed drug survival of individual biologics[2-8], compared drug survival between biologics[9-18] or searched for clinical characteristics that might predict the discontinuation of biologic agents[2-7,9,11,12]. Drug survival is a comprehensive measure of the effectiveness, safety as well as the preferences of both the patient and physician and reflects the probability a patient will stay on the drug over time.[19]

Although drug survival is becoming an increasingly popular outcome measure in biologic treatment of psoriasis, still only a limited number of daily practice studies are available that use prospective data from multiple centres to compare biologic agents.[9-12] Also, several different clinical characteristics have been stated to predict treatment discontinuation in prospective and retrospective studies, but were usually only analysed for treatment discontinuation in general (i.e., overall drug survival) and for all included biologics instead of performing analyses for every biologic separately. This has the potential of missing important predictors, as predictors for discontinuation might differ between different reasons of discontinuation and between biologics.

Among predictors for drug discontinuation in general, female sex is mentioned most often, especially in prospective studies.[2,3,9,11,12,15] Female sex has also been found to predict overall survival of biologic treatment in other inflammatory diseases.[20] Thus far, research into predictors for discontinuation split for ineffectiveness and side-effects has only gained little attention. Moreover, the few studies that have addressed this issue have not been conducted with the same variables at start, leading to a heterogeneity in the selection of candidate predictors.[2,3]

With this study, drug survival of the three biologics was assessed with the aim to elucidate predictors for the drug survival of ADA, ETA and USTE as a group as well as separately per biologic for overall drug survival, drug failure due to ineffectiveness and due to side-effects. The study set out to elucidate the predictors for these most commonly prescribed outpatient biologics in a uniform way, i.e. by selecting the candidate predictors from a set of baseline variables that were similar for each biologic treatment, and to elucidate predictors for different reasons of discontinuation for every biologic separately. This approach might aid physicians in their treatment strategies and increase awareness for those patients at risk of discontinuing that specific biologic treatment.

Methods

BioCAPTURE

BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics) is a registry with prospective clinical practice data on biologic treatment of plaque psoriasis.[10,21] Data from all real-world consecutive patients starting biologic treatment from one academic and eight non-academic centres were included. Patients participating in clinical trials were excluded. BioCAPTURE was approved by the medical ethics committee and, although not mandatory, informed consent was obtained from every patient. Patients with psoriasis were treated according to European and Dutch Guidelines[22,23] and treatment recommendations were made by the treating physician.

Data extraction

Patient characteristics and reason for treatment discontinuation, i.e. ineffectiveness, side-effects or other, were extracted from BioCAPTURE for all patients from inception of the registry (2005) until May 2015. Baseline variables that were extracted were: age at start of biologic, sex, weight, body mass index (BMI) divided into six categories[9] (underweight <18.5; normal weight 18.5-24.99; overweight 25.0-29.99; obese I 30.0-34.99; obese II 35.0-39.99; obese III >40 kg/m^2), positive family history of psoriasis, psoriatic arthritis, duration of psoriasis until start of biologic, baseline PASI score, biologic naivity, antitumour necrosis factor (anti-TNF)-naivity and the presence of at least one comorbidity in medical history (hepatitis B or C, chronic kidney or liver disease, HIV or cancer, except for non-melanoma skin cancer)[2,24] that would have excluded the patient from participating in trials of biologics. When a patient had received different biologics over time, the first treatment episode (TE) of every biologic was used for analysis. In case the patient interrupted the biologic treatment for ≤90 days, the TE was considered to be continuous. Ninety days is a widely accepted maximum interruption period.[9,10,15] All available long-term data were used for drug survival and predictor analyses.

Long-term drug survival analysis

Drug survival was analysed using Kaplan-Meier estimates. An event in the overall survival analysis was defined as every discontinuation of biologic treatment. Additional analyses for the events 'side-effects' and 'ineffectiveness' were also carried out. Censoring was performed for patients still on biologic treatment at the moment of data lock or patients that were lost to follow-up, or for other reasons than the reason of interest.

For USTE the last date plus 8, 10 or 12 weeks, depending on the dosing regimen of the patient was chosen for the primary analyses. Since USTE has a low frequency of

administration and discontinuation date can influence drug survival, a sensitivity analysis was performed with the last date of injection of USTE as the discontinuation date. This conservative approach is presented in the Supplementary file.

Confounder correction for long-term drug survival

Baseline variables were compared between treatment groups using One-Way ANOVA in case of parametric and the Kruskal-Wallis test in case of non-parametric distribution. Categorical variables were compared using the χ^2-test. Significantly different characteristics between ADA, ETA and USTE were corrected for with Multivariate Cox Regression analysis for Drug Survival (MCR-DS) in order to adjust for their possible confounding effect when comparing drug survival between different biologics. Some variables highly correlated and therefore only one variable was chosen for the confounder correction based on p-value; weight was chosen over BMI and biologic-naivity was chosen over anti-TNF-α-naivity. Sex and age at start of the biologic were set as fixed variables. Possible confounders, i.e. the variables that were significantly different between treatment groups, were added as covariates to the MCR-DS. Hazard ratios were extracted from the models and are described.

Predictors for drug survival

To elucidate the predictors for drug survival of ADA, ETA and USTE as a group and separately per biologic for overall drug survival, drug failure due to ineffectiveness and side-effects, firstly all baseline variables were tested with univariate Cox-regression analysis with the p-value set at <0.2. Possible predictor variables were then incorporated in the Multivariate Cox Regression analysis for Predictors (MCR-P; to distinguish this multivariate analysis from the previously mentioned MCR-DS). On the basis of the univariate analysis, BMI was chosen over weight for the multivariate analyses with MCR-P. For the MCR-P backward selection was performed to elucidate the final predictors.

All analyses were performed with IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA). A p-value of <0.05 was considered significant. Variables with a Gaussian distribution were presented as mean ± SD, non-parametrically distributed variables as median [IQR] and categorical data as N(%).

Results

Patients

In total, 526 TEs were included - 186 ADA, 238 ETA and 102 USTE - with a total of 1333 years of treatment. The characteristics of the patient at inclusion in BioCAPTURE are shown in Table 1. The majority of patients were male (60.9%, n=226), overweight

(median BMI 27.8) and had a positive family history of psoriasis (66.0%). Psoriatic arthritis was present in 28.6% of patients. The median PASI score at baseline was 13.2.

Baseline patient characteristics

The baseline patient characteristics per biologic are presented in Table 2. The median baseline weight was significantly higher for USTE (92.0 kg) and ADA (88.0 kg) than for ETA (84.0 kg; p=0.002 and 0.025, respectively). The median baseline BMI was significantly higher for ADA (29.0 kg/m^2) and USTE (28.2 kg/m^2) compared with ETA (27.7 kg/m^2; p= 0.033 and p=0.029, respectively), but not for ADA compared with USTE (p= 0.094). The median baseline PASI score was significantly higher for USTE (13.4) and ETA (13.2) than for ADA (11.1; p=0.007 and p<0.001, respectively). Patients were significantly less often biologic naïve and anti-TNF-α naïve in TEs of USTE compared with ADA (p= 0.004 and p=0.012, respectively) and ETA (p<0.001 in both analyses).

Table 1 Baseline patient characteristics

Baseline patient characteristics	***First ever treatment episode in BioCAPTURE N=371***
Age at start of biologic (yrs)	47.5 ± 12.8 *Missing: 0*
Sex (male)	226 (60.9%) *Missing: 0*
Length (cm)	175.4 ± 8.9 *Missing: 79*
Weight (kg)	86.0 [22.0] *Missing: 75*
BMI (kg/m^2)	27.8 [6.6] *Missing: 79*
Positive family history of psoriasis (yes)	245 (66.0%) *Missing: 13*
Psoriatic arthritis, diagnosis by a Rheumatologist (yes)	106 (28.6%) *Missing: 18*
Duration of psoriasis until start of biologic (yrs)	19.9 [17.6] *Missing: 2*
Baseline PASI score	13.2 [7.7] *Missing: 11*

Mean ± SD, Median [IQR], N(%),yrs: years; PASI: Psoriasis Area and Severity Index.

Table 2 Baseline patient characteristics per biologic

Baseline patient characteristics	***Adalimumab N= 186 patients***	***Etanercept N= 238 patients***	***Ustekinumab N= 102 patients***	***p-value***
Age at start of biologic (yrs)	48.7 ± 12.8 *Missing: 0*	46.9 ± 12.7 *Missing: 0*	50.1 ± 12.5 *Missing: 0*	0.072†
Gender (male)	106 (57%) *Missing: 0*	146 (61.3%) *Missing: 0*	66 (64.7%) *Missing: 0*	0.410¥
Length (cm)	175.5 ± 8.5 *Missing: 16*	174.8 ± 8.5 *Missing: 66*	176.7 ± 8.9 *Missing: 8*	0.223†
Weight (kg)	88.0 [24.0] *Missing: 16*	84.0 [24.3] *Missing: 65*	92.0 [21.2] *Missing: 4*	*0.005*‡
BMI (kg/m^2)	29.0 [6.5] *Missing: 17*	27.7 [3.5] *Missing: 66*	28.2 [6.7] *Missing: 8*	*0.038*‡
Positive family history of psoriasis (yes)	127 (68.3%) *Missing: 6*	154 (64.7%) *Missing: 6*	69 (67.6%) *Missing: 3*	0.637¥
Psoriatic arthritis (yes)	61 (32.8%) *Missing: 7*	71 (29.8%) *Missing: 5*	28 (27.5%) *Missing: 9*	0.329¥
Duration of psoriasis until start of biologic (years)	20.5 [18.4] *Missing: 2*	20.4 [10.5] *Missing: 0*	19.6 [9.6] *Missing: 0*	0.849‡
Baseline PASI score	11.1 [7.2] *Missing: 7*	13.2 [8.2] *Missing: 7*	13.4 [11.5] *Missing: 4*	*<0.001*‡
Biologic naïve (yes)	65 (34.9%) *Missing: 0*	152 (63.9%) *Missing: 0*	19 (18.6%) *Missing: 0*	*<0.001*¥
Anti-TNF-α naïve (yes)	73 (39.2%) *Missing: 0*	174 (73.1%) *Missing: 0*	25 (24.5%) *Missing: 0*	*<0.001*¥

Mean ± SD, Median [IQR], N(%). BMI: Body Mass Index; PASI: Psoriasis Area and Severity Index; TNF: tumour necrosis factor
† One-Way ANOVA, ¥ chi-squared test, ‡ Kruskal Wallis test

Long-term drug survival analysis

All available data on long-term drug survival for ADA, ETA and USTE are shown in Figure 1. During five years of treatment, overall drug survival was in favour of USTE (One year: 84.0% USTE, 75.8% ETA, 74.6% ADA; Five year: 61% USTE, 41% ADA and 34% ETA). Percentages decreased for ADA to 35% at six years and for ETA to 20% at ten years of treatment. Survival rates of drug survival split for ineffectiveness were again in favour of USTE with percentages of 79% for USTE, 54% for ADA and 45% for ETA at five years of treatment. These percentages decreased further for ADA to 50% at six years and for ETA to 31% at ten years. Five-year survival percentages for dis-

continuation due to side-effects were 83% for USTE, 80% for ETA and 76% for ADA. These percentages were 70% for ADA at six years and 70% for ETA at ten years of treatment. Sensitivity analyses yielded similar percentages (see Supplemental material).

Comparing long-term drug survival corrected for confounders

Confounder correction was performed on drug survival analysis by incorporating the significantly different baseline patient characteristics into the Multivariate Cox Regression analysis for Drug Survival (MCR-DS) (Table 2). Age and sex were set as fixed variables. Using all long-term data (see Figure 1), overall drug survival corrected for confounders showed a significantly higher drug survival for USTE when compared with ADA [hazard ratio (HR) 1.743, 95% confidence interval (CI) 1.085 – 2.799] and for USTE compared with ETA [HR 2.155, 95%CI 1.306 – 3.555]. For ADA and ETA, overall survival was similar [HR 0.774, 95%CI 0.560-1.069].

Confounder-corrected drug survival of discontinuation due to ineffectiveness showed a significantly higher survival for USTE when compared with ADA [HR 2.739, 95%CI 1.420 – 5.282] and for USTE compared with ETA [HR 2.908, 95%CI 1.463 – 5.778]. Survival of ADA versus ETA showed no differences [HR 0.798, 95%CI 0.542-1.174].

Confounder-corrected drug survival of discontinuation due to side-effects showed a significantly higher survival for USTE compared with ADA [HR 2.346, 95%CI 1.024 – 5.371] and USTE compared with ETA [HR 2.582, 95%CI 1.022 – 6.522]. Drug survival of ADA compared with ETA was not statistically different [HR 0.927, 95%CI 0.517 – 1.660]. One- and 5-year confounder-corrected drug survival data are presented in the supplement.

Predictors for long-term drug survival

Variables from the univariate analyses that were incorporated in the Multivariate Cox Regression analysis for Predictors (MCR-P) for the different biologics are shown in Supplement_Table 1.

Predictors for ADA, ETA and USTE as one group of biologics. MCR-P for overall survival showed that female sex (hazard ratio (HR) 1.453; 95% confidence interval (95% CI) 1.104-1.916) and higher BMI (HR 1.179; 95% CI 1.041-1.335) were predictors of discontinuation. MCR-P showed that higher BMI (HR 1.252; 95% CI 1.075-1.457) and biologic naivity (HR 1.392; 95% CI 1.003-1.933] were predictors of discontinuation due to ineffectiveness and that female sex (HR 2.825; 95% CI 1.792-4.717) was a predictor of discontinuation due to side-effects.

Predictors for ADA. MCR-P for overall survival as well as for survival due to ineffectiveness yielded no significant predictors. BMI was the last variable in both analyses, but was not significant. MCR-P for side-effects showed that female sex (HR 2.907; 95% CI 1.348-6.289) was a predictor of discontinuation.

Predictors for ETA. Female sex (HR 1.767; 95% CI 1.183-2.639), higher BMI (HR 1.252; 95% CI 1.039-1.509) and the presence of specific comorbidities (HR 1.894; 95% CI 1.036-3.460) were predictors of overall discontinuation. MCR-P showed that higher BMI (HR 1.339; 95% CI 1.066-1.682) was a predictor for discontinuation due to ineffectiveness. Female sex (HR 2.326; 95% CI 1.012-5.348), higher BMI (HR 1.466; 95% CI 1.007-2.077) and age at start of ETA treatment (HR 1.422; 95% CI 1.055-1.917) were predictors for discontinuation due to side-effects.

Predictors for USTE. MCR-P showed that higher BMI (HR 1.429; 95% CI 1.008-2.028) was a predictor for overall survival. Higher BMI (HR 1.977; 95% CI 1.218-3.210) was a predictor for discontinuation due to ineffectiveness and female sex (HR 4.016; 95% CI 1.003-16.129) was a predictor of discontinuation due to side-effects. In the group of patients with bodyweight >100kg who failed USTE due to ineffectiveness, five (83%) of six patients were treated with 90mg and were thus treated according to the guidelines.[22,23]

Side-effects resulting in discontinuation of the biologic agent in female and male patients

In total 79 patients discontinued their biologic treatment due to side-effects; 30 (38%) for ADA, 40 (51%) for ETA and 9 (11%) for USTE. Side-effects per biologic are presented in Supplement_Table 2. Forty-five (57%) of 79 patients were female. Number (percentage) of female/male patients with side-effects leading to treatment discontinuation was 20 (25%)/ 10 (9.4%) for ADA, 19 (20.7%)/ 21 (14.4%) for ETA and 6 (16.7%)/ 3 (4.5%) for USTE. There was a heterogeneity in experienced side-effects and no pattern in type of side-effect was found between female and male patients. Infections, mainly of the respiratory tract, were a common reason for discontinuing ADA and ETA, but not USTE treatment. There were also no patterns found for infections between female and male patients, nor between ADA and ETA. The only side-effects that could be characterized as typical for female patients were a cystitis in one female patient during ADA treatment, breast cancer in one female patient on ETA treatment and cervical cancer in one female patient on ETA treatment. One female patient on ADA treatment and one male patient on ETA treatment stopped their treatment due to feelings of depression.

Biologic dose

The mean±SD cumulative dose of the biologics was 2783±2353mg for ADA, 9720±8746mg for ETA and 632±587mg for USTE (ADA: 50±18mg per 2 weeks; ETA: 76±18 mg per week, USTE≤100kg: 69±32mg per 12 weeks; USTE>100kg: 97mg± 38mg per 12 weeks). In our cohort, patients treated with ADA and ETA more often had a dose increase (i.e., a higher dose than the recommended label dose) compared with patients treated with USTE (ADA 40%; ETA 69%; USTE 27% of patients).

Figure 1 Ten-year drug survival for adalimumab, etanercept and ustekinumab

Figure 1A Ten-year overall drug survival for adalimumab, etanercept and ustekinumab.

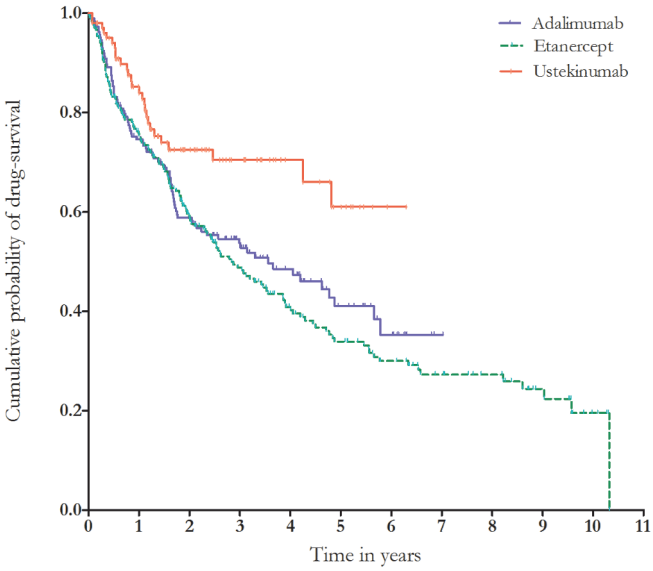


Figure 1B Ten-year drug with discontinuation due to ineffectiveness split per biologic.

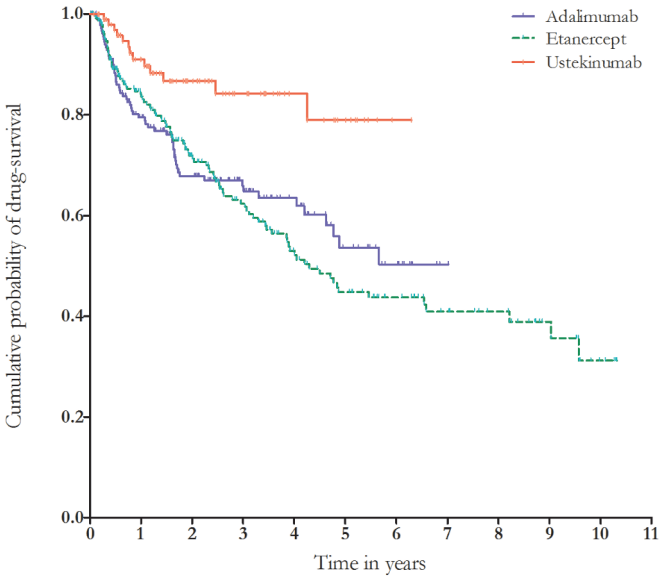
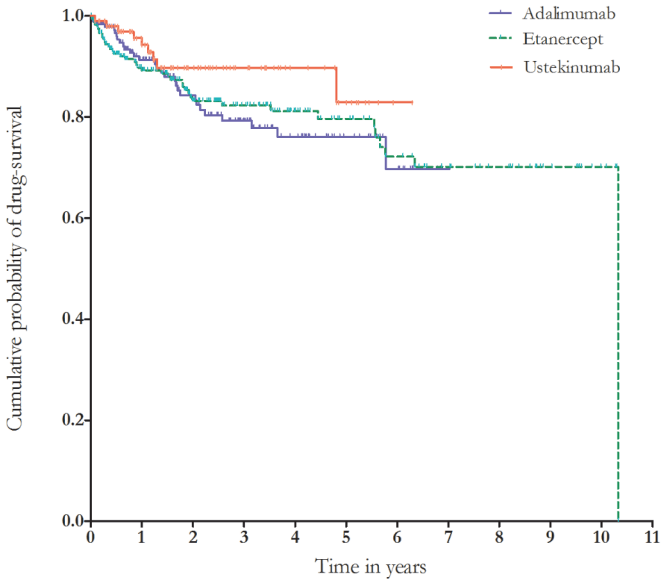


Figure 1C Ten-year drug with discontinuation due to side-effects split per biologic.



Discussion

This prospective, comparative, multicenter, long-term drug survival study showed that a higher BMI was a predictor for drug discontinuation due to ineffectiveness for ETA and USTE and that female sex was a consistent predictor for discontinuation due to side-effects for ADA, ETA as well as USTE. USTE had the highest confounder-corrected long-term drug survival in psoriasis treatment, compared with ADA and ETA. Consistently with our study, a higher BMI was previously found to predict overall biologic discontinuation in psoriasis treatment.[25-27] BMI was also a predictor of overall biologic survival in patients with rheumatoid arthritis.[28] However, overall biologic survival is a result of drug discontinuation due to ineffectiveness, side-effects and other reasons.[19] Of these, ineffectiveness is the main reason for discontinuation of biologics in psoriasis treatment.[9,11] Highlighting the predictors for ineffectiveness is therefore of interest. Our study elucidated that a higher BMI is a predictor of biologic discontinuation due to ineffectiveness for ETA as well as USTE, but was not a significant predictor for drug survival of ADA. Given the current results from different

studies, one might consider that patients with psoriasis with a higher BMI should be encouraged to lose weight before and during their biologic treatment. Indeed, a recently performed randomized controlled trial showed a positive effect of a diet-exercise combination over an information-only strategy on psoriasis severity in patients with who were being treated with systemic agents such as biologics.[29] In another randomized trial, psoriasis severity was significantly lower in the diet group than in the control group at 24 weeks of biologic treatment.[30]

Previous studies on overall drug survival of biologics as a group have stated that female sex was a predictor for biologic discontinuation in psoriasis treatment.[2,3,9,11,12,15] Also, in rheumatoid arthritis and in axial spondyloathritis, female sex predicted overall drug discontinuation of anti-TNF-α therapies grouped together.[20,31] So far, only one study on predictors highlighted ADA treatment for psoriasis by using data from a smaller BioCAPTURE cohort and found that female sex was a predictor for ADA discontinuation due to side-effects.[2] Our present study with extended data from BioCAPTURE shows that female sex is a predictor for drug discontinuation due to side-effects for ADA, ETA as well as USTE in psoriasis treatment. The exact reason behind this is unclear. No different pattern in type or severity of side-effects was found between female and male patients in our study. The fact that female sex is a predictor in all three biologics suggests that there is no class-effect and that other reasons should be considered. For example, although scarce, publications on this topic have demonstrated gender differences in the presentation of symptoms, prognosis of diseases and treatment outcomes as well as in communication.[32] In a study regarding hospital in-patients it was shown that severe adverse drug reactions were seen more often in women than men.[33] Regardless of the underlying reason, our results can increase the awareness of physicians that female patients have a higher chance of discontinuing biologic therapy for psoriasis due to side-effects compared with male patients.

There are several studies that have assessed biomarkers in order to predict treatment success for the individual patient, such as genetic, blood or tissue biomarkers.[34] Patient characteristics, however, can also serve as predictors for treatment success. Our analyses contribute to the first steps of developing a predictor model for biologic treatment in psoriasis. Other large prospective studies are needed to confirm our results.

So far, only a small number of daily practice studies have used prospective data from multiple centres to compare biologic agents.[9-12] Similar to findings in these studies, our study with long-term data showed that USTE had the highest confounder-corrected overall drug survival compared with both ADA and ETA. Unique in our study is the confounder-corrected drug survival split for discontinuation due to ineffectiveness and side-effects. Again, USTE had the highest drug survival in both analyses compared with ADA and ETA. Moreover, infliximab and not USTE was the last resort

biologic for psoriasis treatment in this study. Also, doses were more often higher than label dose for ETA>ADA>USTE. We did not expect that the missing data on weight had a major influence on our presented confounder-corrected drug survival outcomes, since ETA had more cases in total compared with USTE. Indeed, our results were similar when missing data on weight were imputed by the median weight of patients for that biologic. Our data, together with data from previous studies, might aid physicians in their choice of long-term biologic treatment for patients with psoriasis.

A limitation of our study is the lower number of patients when compared with nation-wide registries from larger countries.[9] Strengths of our study are the detailed documentation of patient characteristics in our registry, the multicenter and prospective setting as well as the performed drug survival analyses split for every biologic and split for reasons of discontinuation. Furthermore, candidate predictors were chosen from baseline variables that were similar for every biologic, increasing the homogeneity in analysis.

In conclusion, this prospective, comparative, multicenter, long-term drug survival study shows that higher BMI is a predictor for drug discontinuation due to ineffectiveness for ETA and USTE and that female sex is a consistent predictor for discontinuation due to side-effects for ADA, ETA as well as USTE. Furthermore, USTE has the highest confounder-corrected long-term drug survival. Comparative results from the long-term drug survival aid the physician in choosing the most-suited long-term treatment for their individual patients with psoriasis. Our data also help to increase the awareness among physicians that higher BMI influences drug survival in ETA and USTE, and that female patients are prone to discontinuation of ADA, ETA as well as USTE because of side-effects.

Supplemental material

Sensitivity analysis for drug survival uncorrected for confounders

Sensitivity analysis with USTE last date of injection (Supplement_Figure 1 to 3). Overall drug survival percentages after five years were USTE 63%, ADA 41% and ETA 34%. Percentages were 35% for ADA after six years, and 20% for ETA after ten years. Five-year survival rates of discontinuation due to ineffectiveness were 80%, 54% and 45% for USTE, ADA and ETA, respectively. These were 50% for ADA after six years and 31% for ETA after ten years. Five-year survival percentages for discontinuation due to side-effects were 84% for USTE, 80% for ETA and 76% for ADA. These percentages were 70% for ADA after six years and 70% for ETA after ten years.

Sensitivity analysis for drug survival corrected for confounders

Sensitivity analysis with USTE last date of injection. All available long-term data were used for drug survival analyses. Overall drug survival showed a higher drug survival for USTE when compared with ADA [hazard ratio (HR) 1.689, 95% confidence interval (CI) 1.051 – 2.713] and for USTE compared with ETA [HR 2.079, 95%CI 1.261 – 3.428]. For ADA and ETA, overall survival was similar [HR 0.774, 95%CI 0.560-1.069]. Confounder-corrected drug survival of discontinuation due to ineffectiveness showed a higher survival for USTE when compared with ADA [HR 2.634, 95%CI 1.365 – 5.083] and for USTE compared with ETA [HR 2.792, 95%CI 1.406 – 5.541]. Survival of ADA versus ETA showed no differences [HR 0.798, 95%CI 0.542-1.174]. Confounder-corrected drug survival of discontinuation due to side-effects showed a higher survival of USTE when compared with ADA [HR 2.295, 95%CI 1.002 – 5.260] and USTE compared with ETA [HR 2.470, 95%CI 0.980 – 6,224]. Drug survival of ADA compared with ETA was not statistically different [HR 0.927, 95%CI 0.517 – 1.660].

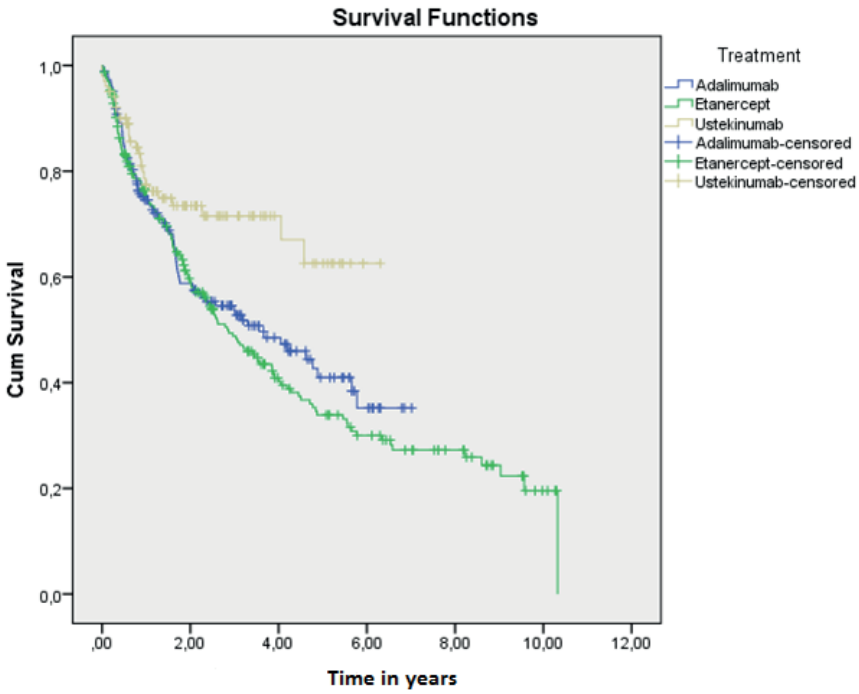
Confounder corrected drug survival analysis at one year and five years of biologic treatment

Overall drug survival corrected for confounders showed a trend towards a higher drug survival for USTE when compared with ADA at one year [hazard ratio (HR) 1.766, 95% confidence interval (CI) 0.924 – 3.378] and a significantly higher drug survival for USTE when compared with ADA at five years [HR 1.731, 95%CI 1.077 – 2.784]. Overall drug survival corrected for confounders showed a higher drug survival for USTE compared with ETA at one and five years [one year: HR 3.132, 95%CI 1.533 – 6.401; five years: HR 2.214, 95%CI 1.337 – 3.667]. Survival of ADA versus ETA showed no differences [one year: HR 0.881, 95%CI 0.551 – 1.407; five years: HR 0.769, 95%CI 0.553 – 1.069].

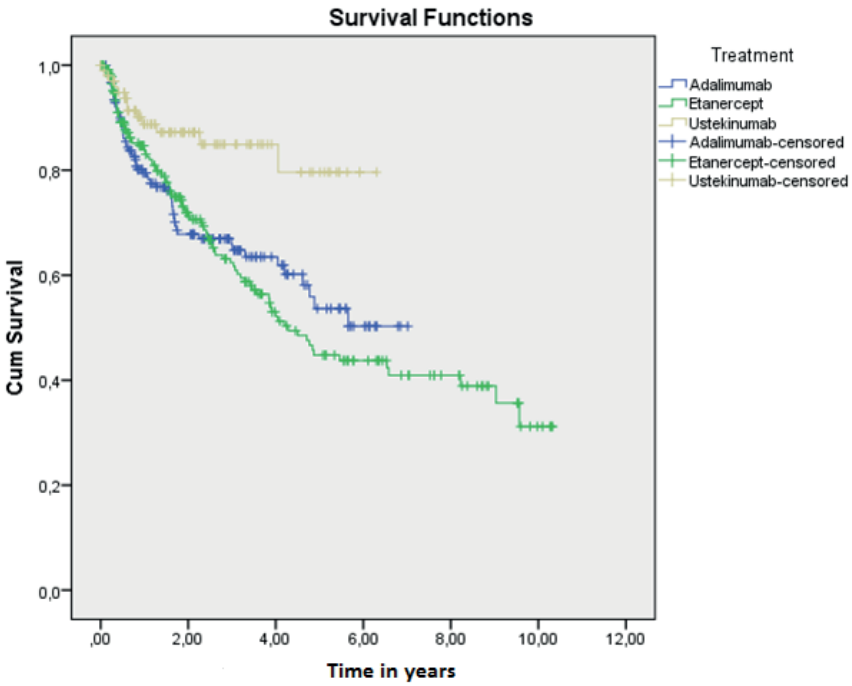
Confounder-corrected drug survival of discontinuation due to ineffectiveness showed a significantly higher survival for USTE when compared with ADA [one year: HR

2.773, 95%CI 1.184 – 6.493; five years: HR 2.716, 95%CI 1.407 – 5.242] and for USTE compared with ETA [one year: HR 3.524, 95%CI 1.354 – 9.172; five years: HR 3.033, 95%CI 1.525-6.032]. Survival of ADA versus ETA showed no differences [one year: HR 1.028, 95%CI 0.595 – 1.776; five years: HR 0.787, 95%CI 0.533 – 1.163].
Confounder-corrected drug survival of discontinuation due to side-effects showed a similar drug survival of USTE compared with ADA at one year (HR 2.344; 0.718-7.652], a significantly higher survival of USTE when compared with ADA at five years [HR 2.345, 95%CI 1.019 – 5.395] and a higher survival for USTE compared with ETA at both one and five years of treatment [one year: HR 4.748, 95%CI 1.325 – 17.022; five years: HR 2.645, 95%CI 1.017 – 6.877]. Drug survival of ADA compared with ETA was not statistically different at both one and five years of treatment [one year: HR 0.777, 95%CI 0.346 – 1.742; five years: HR 0.965, 95%CI 0.525 – 1.774].

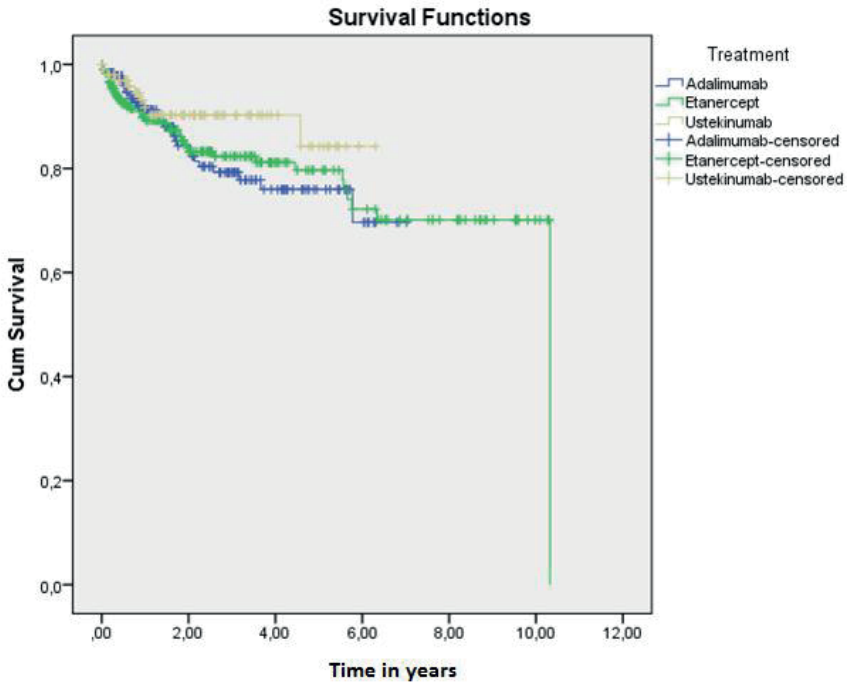
Supplement_Figure 1 Ten-year overall drug survival with USTE last date of injection



Supplement_Figure 2 Ten-year drug survival with discontinuation due to ineffectiveness – sensitivity analysis with USTE last date of injection



Supplement_Figure 3 Ten-year drug survival with discontinuation due to side-effects – sensitivity analysis with USTE last date of injection



Supplement_Table 1 Variables selected as possible predictors from univariate Cox-regression analyses

	ADA,ETA and USTE together *Overall drug survival*	**ADA, ETA and USTE together** *Drug survival with discontinuation due to ineffectiveness*	**ADA, ETA and USTE together** *Drug survival with discontinuation due to side-effects*	**ADA** *Overall drug survival*
Age at start of biologic₸	0.994 [0.901-1.010]	0.994 [0.881-1.121]	**1.129 [0.945-1.350]**	1.035 [0.878-1.221]
Sex (Female)	**1.531 [1.198-1.956]**	**1.359 [1.004-1.839]**	**2.369 [1.516-3.703]**	**1.430 [0.943-2.169]**
Trial eligible† (No)	1.234 [0.843-1.806]	**1.533 [0.995-2.360]**	**1.533 [0.995-2.360]**	1.097 [0.550-2.187]
Weight‡	**1.009 [1.002-1.017]**	**1.010 [1.001-1.019]**	**1.013 [1.000-1.026]**	1.007 [0.996-1.018]
BMI¥	**1.219 [1.074-1.383]**	**1.258 [1.082-1.463]**	**1.311 [1.044-1.646]**	**1.191 [0.978-1.450]**
Family history of psoriasis (No)	0.945 [0.722-1.236]	1.084 [0.786-1.496]	0.803 [0.485-1.327]	0.778 [0.483-1.252]
Diagnosis of PSA (No)	0.995 [0.764-1.296]	0.903 [0.656-1.243]	1.195 [0.728-1.962]	1.085 [0.696-1.691]
Duration of psoriasis$	**0.905 [0.881-1.009]**	0.942 [0.825-1.075]	0.891 [0.732-1.085]	1.011 [0.856-1.194]
Baseline PASI§	0.996 [0.980-1.013]	1.004 [0.984-1.024]	0.994 [0.965-1.025]	0.979 [0.941-1.018]
Biologic naïvefl (No)	0.908 [0.711-1.160]	**0.779 [0.577-1.050]**	1.240 [0.789-1.948]	**1.386 [0.860-2.233]**
Anti-TNF-α naïve (No)	0.890 [0.697-1.136]	**0.785 [0.581-1.063]**	1.039 [0.668-1.615]	**1.371 [0.867-2.170]**

Numbers are presented as hazard ratio [95% confidence intervals]. Bold hazard ratios had a P-value of <0.2.

₸ Age in 10 year intervals

† Trial eligible: patients were trial eligible if they did not have a prior history of hepatitis B or C, chronic kidney or liver disease, HIV or cancer, except for non-melanoma skin cancer.

‡ For the multivariate model, BMI was chosen instead of weight.

¥ Body Mass Index is divided into underweight (<18.5 kg/m^2); normal weight (18.5-24.99 kg/m^2), overweight 25-29.99 kg/m^2), obese I (30-34.99 kg/m^2), obese II (35-39.99 kg/m^2) and obese III (>40 kg/m^2).

$ Duration of psoriasis until start of biologic in 10 year intervals

§ PASI: psoriasis area and severity index

fl For the multivariate model, biologic naïve was chosen instead of anti-TNF-α naïve

	ADA *Drug survival with discontinuation due to ineffectiveness*	**ADA** *Drug survival with discontinuation due to side-effects*	**ETA** *Overall drug survival*	**ETA** *Drug survival with discontinuation due to ineffectiveness*	**ETA** *Drug survival with discontinuation due to side-effects*
	1.062 [0.872-1.294]	1.056 [0.795-1.404]	1.012 [0.883-1.160]	0.871 [1.014-0.859-1.197]	**1.141 [0.885-1.470]**
	1.410 [0.856-2.322]	**3.143 [1.468-6.728]**	**1.517 [1.089-2.114]**	1.285 [0.854-1.934]	**1.748 [0.937-3.259]**
	1.675 [0.826-3.398]	**1.675 [0.826-3.398]**	**1.467 [0.894-2.405]**	1.432 [0.782-2.623]	1.432 [0.782-2.623]
	1.005 [0.992-1.019]	1.007 [0.989 – 1.026]	**1.014 [1.003-1.026]**	**1.017 [1.004-1.031]**	**1.023 [1.002-1.045]**
	1.199 [0.949-1.516]	**1.297 [0.944-1.783]**	**1.285 [1.058-1.560]**	**1.339 [1.066-1.682]**	**1.528 [1.068-2.188]**
	0.860 [0.491-1.505]	**0.433 [0.166-1.133]**	1.077 [0.756-1.536]	1.276 [0.839-1.939]	1.065 [0.547-2.074]
	1.043 [0.612-1.778]	0.962 [0.454-2.037]	1.057 [0.739-1.513]	0.883 [0.579-1.346]	**1.809 [0.831-3.935]**
	1.060 [0.872-1.289]	0.997 [0.748-1.330]	**0.771 [0.655-0.908]**	**0.792 [0.649-0.966]**	**0.792 [0.586-1.071]**
	0.999 [0.995-1.046]	0.970 [0.907-1.038]	1.004 [0.983-1.024]	1.008 [0.984-1.033]	0.999 [0.961-1.038]
	1.394 [0.787-2.466]	1.598 [0.682-3.742]	0.903 [0.640-1.274]	**0.716 [0.464-1.105]**	1.285 [0.685-2.410]
	1.392 [0.803-2.414]	1.327 [0.605-2.910]	0.785 [0.532-1.157]	**0.645 [0.393-1.059]**	0.881 [0.430-1.806]

Supplement_Table 1 Continued

	USTE *Overall drug survival*	**USTE** *Drug survival with discontinuation due to ineffectiveness*	**USTE** *Drug survival with discontinuation due to side-effects*
Age at start of biologic₸	0.926 [0.676-1.268]	0.804 [0.511-1.265]	**1.618 [0.891-2.939]**
Sex (Female)	**2.128 [0.999-4.530]**	1.668 [0.560-4.968]	**4.024 [1.005-16.108]**
Trial eligible† (No)	1.042 [0.312-3.481]	**2.553 [0.698-9.339]**	**2.553 [0.698-9.339]**
Weight‡	**1.020 [0.996-1.045]**	**1.036 [1.001-1.071]**	0.991 [0.948-1.036]
BMI¥	**1.429 [1.008-2.028]**	**1.977 [1.218-3.210]**	0.728 [0.342-1.553]
Family history of psoriasis (No)	0.951 [0.410-2.207]	1.148 [0.334-3.938]	1.213 [0.289-5.088]
Diagnosis of PSA (No)	0.598 [0.259-1.383]	0.668 [0.195-2.284]	0.650 [0.155-2.725]
Duration of psoriasis$	1.024 [0.748-1.402]	1.038 [0.665-1.619]	0.881 [0.486-1.594]
Baseline PASI§	0.997 [0.949-1.047]	1.013 [0.948-1.083]	1.038 [0.959-1.124]
Biologic naïvefl (No)	0.927 [0.348-2.469]	0.701 [0.191-2.577]	1.659 [0.204-13.495]
Anti-TNF-α naïve (No)	1.428 [0.539-3.785]	1.081 [0.296-3.945]	2.548 [0.316-20.551]

Numbers are presented as hazard ratio [95% confidence intervals]. Bold hazard ratios had a P-value of <0.2.

₸ Age in 10 year intervals

† Trial eligible: patients were trial eligible if they did not have a prior history of hepatitis B or C, chronic kidney or liver disease, HIV or cancer, except for non-melanoma skin cancer.

‡ For the multivariate model, BMI was chosen instead of weight.

¥ Body Mass Index is divided into underweight (<18.5 kg/m^2); normal weight (18.5-24.99 kg/m^2), overweight 25-29.99 kg/m^2), obese I (30-34.99 kg/m^2), obese II (35-39.99 kg/m^2) and obese III (>40 kg/m^2).

$ Duration of psoriasis until start of biologic in 10 year intervals

§ PASI: psoriasis area and severity index

fl For the multivariate model, biologic naïve was chosen instead of anti-TNF-α naïve

Supplement_Table 2 Side-effects leading to discontinuation of biologic reported per agent

Side-effect leading to treatment discontinuation	*Adalimumab N= 186 patients*		*Etanercept N=238*		*Ustekinumab N=102*	
	80 ♀	**106 ♂**	**92 ♀**	**146 ♂**	**36 ♀**	**66 ♂**
Infection[a]	7 (3.8%)	5 (4.7%)	5 (5.4%)	4 (2.7%)	0	0
Inflammation	1 (1.3%)	0	1 (1.1%)	3 (2.1%)	0	0
Auto-immune disorder	0	0	0	1[b] (0.7%)	0	0
Laboratory abnormalities	0	1[c] (0.9%)	0	1[d] (0.7%)	1[e] (2.8%)	0
Psychological / mood disorder	1 (1.3%)	0	0	1 (0.7%)	0	0
Neoplasm, malign	2[f] (2.5%)	0	4[g] (4.3%)	3[h]	0	2[i] (3.0%)
Drug reaction	3 (3.8%)	0	1 (1.1%)	0	0	1 (1.5%)
Change of type of psoriasis	2 (2.5%)	0	0	0	0	0
Ophthalmology	1[j] (1.3%)	0	0	0	0	0
Otology	1[k] (1.3%)	0	0	0	0	0
Dermatology[L]	1 (1.3%)	0	1 (1.1%)	1 (0.7%)	2 (5.6%)	0
Musculoskeletal[m]	1 (1.3%)	1 (0.9%)	0	0	0	0
Cardiovascular	0	1[n] (0.9%)	0	3[o] (2.1%)	2[p] (5.6%)	0
Pulmonary[q]	0	1 (0.9%)	2 (2.2%)	0	0	0
Gastro-intestinal[r]	0	0	2 (2.2%)	1 (0.7%)	0	0
Renal	0	0	1[s] (1.1%)	0	0	0
Malaise	0	1 (0.9%)	1 (1.1%)	2 (1.4%)	1 (2.8%)	0
Injection-site reaction	0	0	1 (1.1%)	1 (0.7%)	0	0

[a] e.g., upper respiratory tract infection, flu, pneumonia, cystitis, tuberculosis
[b] Stage II sarcoïdosis
[c] p-ANCA positivity
[d] leucopenia, neutropenia, trombopenia
[e] increase of ALAT and yGT
[f] basal cell carcinoma (2 patients)
[g] Cervical carcinoma (one patient), squameus cell carcinoma and basal cell carcinoma (one patient), breast cancer (one patient), lung cancer (one patient)
[h] Esophageal cancer (one patient), superficial spreading melanoma (one patient), multiple myeloma (one patient)
[i] Renal cell carcinoma (one patient), bladder cancer (one patient)
[j] Dry eyes
[k] Progressive hear loss
[L] e.g., worsening of pre-existing hidradenitis suppurativa, Grover's disease, itch
[m] e.g., muscle pain
[n] Hypertension
[o] myocardial infarction (one patient), heart failure (one patient), heart rhythm disorder (one patient)
[p] hypertension (one patient), cerebrovascular accident (one patient)
[q] e.g. dyspnea, persistent coughing without signs of an infection
[r] e.g., nausea, diarrhea
[s] nephrotic syndrome

References

1 Nast A, Jacobs A, Rosumeck S et al. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. J Invest Dermatol 2015.

2 van den Reek JM, Tummers M, Zweegers J et al. Predictors of adalimumab drug survival in psoriasis differ by reason for discontinuation: long-term results from the Bio-CAPTURE registry. J Eur Acad Dermatol Venereol 2015; 29: 560-5.

3 van den Reek JM, van Lumig PP, Driessen RJ et al. Determinants of drug survival for etanercept in a long-term daily practice cohort of patients with psoriasis. Br J Dermatol 2014; 170: 415-24.

4 Puig L, Ruiz-Salas V. Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis. Dermatology 2015; 230: 46-54.

5 Spertino J, Lopez-Ferrer A, Vilarrasa E et al. Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. J Eur Acad Dermatol Venereol 2014; 28: 1514-21.

6 Lopez-Ferrer A, Vilarrasa E, Gich IJ et al. Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single Spanish centre. Br J Dermatol 2013; 169: 1141-7.

7 Esposito M, Gisondi P, Cassano N et al. Treatment adherence to different etanercept regimens, continuous vs. intermittent, in patients affected by plaque-type psoriasis. Drug Dev Res 2014; 75 Suppl 1: S31-4.

8 Clemmensen A, Spon M, Skov L et al. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol 2011; 25: 1037-40.

9 Warren RB, Smith CH, Yiu ZZ et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol 2015.

10 van den Reek JM, Zweegers J, Kievit W et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. Br J Dermatol 2014; 171: 1189-96.

11 Gniadecki R, Bang B, Bryld LE et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol 2015; 172: 244-52.

12 Gniadecki R, Kragballe K, Dam TN et al. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol 2011; 164: 1091-6.

13 Menting SP, Sitaram AS, Bonnerjee-van der Stok HM et al. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. Br J Dermatol 2014; 171: 875-83.

14 Ross C, Marshman G, Grillo M et al. Biological therapies for psoriasis: Adherence and outcome analysis from a clinical perspective. Australas J Dermatol 2016; 57: 137-40.

15 Esposito M, Gisondi P, Cassano N et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. Br J Dermatol 2013; 169: 666-72.

16 Umezawa Y, Nobeyama Y, Hayashi M et al. Drug survival rates in patients with psoriasis after treatment with biologics. J Dermatol 2013; 40: 1008-13.

17 Brunasso AM, Puntoni M, Massone C. Drug survival rates of biologic treatments in patients with psoriasis vulgaris. Br J Dermatol 2012; 166: 447-9.

18 Inzinger M, Wippel-Slupetzky K, Weger W et al. Survival and Effectiveness of Tumour Necrosis Factor-alpha Inhibitors in the Treatment of Plaque Psoriasis under Daily Life Conditions: Report from the Psoriasis Registry Austria. Acta Derm Venereol 2015.

19 van den Reek JM, Kievit W, Gniadecki R et al. Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls. J Invest Dermatol 2015; 135: e34.

20 Gulfe A, Kapetanovic MC, Kristensen LE. Efficacy and drug survival of anti-tumour necrosis factor-alpha therapies in patients with non-radiographic axial spondyloarthritis: an observational cohort study from Southern Sweden. Scand J Rheumatol 2014; 43: 493-7.

21 Zweegers J, van den Reek JM, van de Kerkhof PC et al. Comparing treatment goals for psoriasis with treatment decisions in daily practice: results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE. Br J Dermatol 2014; 171: 1091-8.
22 Zweegers J, de Jong EM, Nijsten TE et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatol Online J 2014; 20.
23 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009; 23 Suppl 2: 1-70.
24 Garcia-Doval I, Carretero G, Vanaclocha F et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol 2012; 148: 463-70.
25 Di Lernia V, Tasin L, Pellicano R et al. Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis. J Dermatolog Treat 2012; 23: 404-9.
26 Naldi L, Addis A, Chimenti S et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. Dermatology 2008; 217: 365-73.
27 Carrascosa JM, Vilavella M, Garcia-Doval I et al. Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. J Eur Acad Dermatol Venereol 2014; 28: 907-14.
28 Iannone F, Fanizzi R, Notarnicola A et al. Obesity reduces the drug survival of second line biological drugs following a first TNF-alpha inhibitor in rheumatoid arthritis patients. Joint Bone Spine 2015; 82: 187-91.
29 Naldi L, Conti A, Cazzaniga S et al. Diet and physical exercise in psoriasis: a randomized controlled trial. Br J Dermatol 2014; 170: 634-42.
30 Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert Opin Biol Ther 2014; 14: 749-56.
31 Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford) 2015.
32 Teunissen TA, Rotink ME, Lagro-Janssen AL. Gender differences in quality of care experiences during hospital stay: A contribution to patient-centered healthcare for both men and women. Patient Educ Couns 2015.
33 Davies EC, Green CF, Taylor S et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009; 4: e4439.
34 Villanova F, Di Meglio P, Nestle FO. Biomarkers in psoriasis and psoriatic arthritis. Ann Rheum Dis 2013; 72 Suppl 2: ii104-10.

PART IV

IMPROVING EFFICACY AND EFFECTIVENESS

10

Summary of the Dutch S3-Guidelines on the treatment of psoriasis 2011

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Abstract

This document provides a summary of the Dutch S3-guidelines on the treatment of psoriasis. These guidelines were finalized in December 2011 and contain unique chapters on the treatment of psoriasis of the face and flexures, childhood psoriasis as well as the patient's perspective on treatment. They also cover the topical treatment of psoriasis, photo(chemo)therapy, conventional systemic therapy and biological therapy.

Introduction to the guidelines

J. Zweegers, E.M.G.J. de Jong, Ph.I. Spuls

1.1 Short introduction to psoriasis

Psoriasis is a chronic, inflammatory skin disease with a prevalence of 2-3% in the Western population [1, 2]. The most common clinical form of psoriasis is the chronic plaque type (90%). Abnormalities of the nails are seen in 50-80% of patients with psoriasis and 20-30% also suffer from psoriatic arthritis. Other subtypes are inverse/genital, facial, scalp, guttate, erythrodermic, pustular, and palmoplantar psoriasis. Patients with psoriasis have strongly reduced quality of life scores with a quality of life similar to patients with diabetes mellitus, cardiovascular diseases, breast cancer, and depression [3]. Psoriasis is a disease that reaches further than the skin and may have systemic symptoms, such as metabolic syndrome. It may be associated with other chronic inflammatory diseases such as Crohn's disease, rheumatoid arthritis, and diabetes mellitus [4]. In psoriasis an abnormal local immune reaction can be seen, with a significantly elevated number of activated T-cells and dendritic cells and an enhanced production of cytokines. Cytokines that appear in large numbers in psoriatic lesions are TNF-alpha, type 1 and type 2 interferons, IL-12, IL-22, IL-23, and IL-17A [1, 5].

Therapies for psoriasis available in the Netherlands include topical treatments (corticosteroids, calcineurin inhibitors, Vitamin D3 analogues, coal tar, dithranol, combination preparations), photo(chemo)therapy (UVB, PUVA), and systemic therapies. The conventional systemic therapies include methotrexate, cyclosporine, acitretin, and fumaric acid esters. In targeting specific elements of the immune system, biologics have been added to the therapeutic armamentarium relatively recently. These expensive drugs are indicated for patients with moderate to severe psoriasis after ineffective phototherapy, methotrexate, or cyclosporine therapy or when these more common therapies are contraindicated or not being tolerated. Of the biologics, infliximab and adalimumab are antibodies against TNF-alpha and etanercept is a soluble TNF-alpha receptor fusion protein. Ustekinumab is a monoclonal antibody against the IL-12/IL-23 p40 protein.

1.2 Update of the Dutch S3-guidelines on the treatment of psoriasis

In 2003, the Dutch Society of Dermatology and Venereology introduced the first evidence-based guidelines on the treatment of psoriasis [6]. In 2006-2007, Germany published their first guidelines based on the Dutch guidelines of 2003 [7]. In 2009, the European S3-guidelines from the European Dermatology Forum appeared in the literature and were based on the Dutch, British, and German S3-guidelines [8].

In 2005, the Dutch Society of Dermatology and Venereology updated the practice guidelines from 2003 by updating the literature and including biologics to the guidelines. In 2009, these guidelines were revised slightly, specifically to improve the safety around prescribing methotrexate.
In 2011, the Dutch Society of Dermatology and Venereology finalized a complete update of the S3-guidelines on the treatment of psoriasis in Dutch, which is available online (Dutch S3-Guidelines on the Treatment of Psoriasis 2011; http://www.huidarts.info/documents/uploaded_file.aspx?id=579). Besides an update of the chapters on topical therapy, phototherapy, conventional systemic therapy, and biologic therapy for chronic plaque type psoriasis, these guidelines contain new chapters on the treatment of psoriasis of the face and flexures, childhood psoriasis, and the patient's perspective on treatment. The European S3-guidelines on the systemic treatment of psoriasis vulgaris by Pathirana, et al. (2009) were used as a basis for the Dutch S3-guidelines on the treatment of psoriasis 2011. We will summarize these Dutch S3-guidelines in this article.
Also in 2011, the Dutch Society for Rheumatology initiated additional, multidisciplinary guidelines (Dutch society of Rheumatology, Dermatology and Venereology, Gastro-enterology and Hepatology, Physicians for Pulmonology and Tuberculosis and Internal Medicine as well as the Dutch Arthritis Association) on the use of biologics in daily practice [9] (http://www.reumabond.nl/downloads/algemeen/Mijn%20leven/Medicijnen/Biologicals/Richtlijn_biologicals_geautoriseerd.pdf). These multidisciplinary guidelines answer questions on commonly encountered issues relating to treatment with biologics. Topics include pregnancy, surgical procedures, travelling abroad, and vaccination. We will not discuss these guidelines here.

1.3 Goals of the guidelines

The Dutch S3-guidelines on treatment of psoriasis 2011 contain recommendations in order to aid decision-making on treatment of psoriasis in daily practice. The guidelines are based on systematic reviews, primary research, and expert opinions. The guidelines are intended for dermatologists, but other personnel involved in treating psoriasis, such as general practitioners, could also benefit from it.

1.4 Composition of the working group

Dermatologists as well as patient representatives participated in the working group. Academic and peripheral centers had to be equally represented. These guidelines were developed independently of pharmaceutical companies. Conflicts of interest of working group members are mentioned within these guidelines.

1.5 Methods

The working group worked for two consecutive years (8 meetings) on a draft of the Dutch S3-guidelines. The working group formulated several key questions, which in combination with the chapters of the European S3-guidelines (Pathirana et al. 2009), served as the framework for these guidelines. Existing chapters of the European S3-guidelines were translated and updated. Chapters on the treatment of psoriasis of the face and flexures and on the treatment of childhood psoriasis were based on additional, separate systematic reviews (10-12). The search strategies executed to develop these guidelines are stated in appendix 1 of the Dutch S3-guidelines (appendix 1 of the Dutch S3-guidelines, available online: http://www.huidarts.info/documents/uploaded_file.aspx?id=579).

An assessment and literature evaluation form were used to select the relevant literature (appendix 2 of the Dutch S3-guidelines, available at http://www.huidarts.info/documents/uploaded_file.aspx?id=579). A full text version of the relevant studies was requested. Subsequently, these studies were selected according to inclusion and exclusion criteria and methodological quality (Table 1). Grades of evidence (GE) were assessed for selected articles (Table 2). Then, the members of the working group formulated conclusions and treatment recommendations based on included studies and provided these conclusions with an evidence level (Table 2). The final chapters were discussed and the concept guidelines were published online. Dermatologists were able to provide additional comments. These comments were implemented in the final version of the guidelines and approved by the Dutch Society of Dermatology and Venereology in December 2011.

1.6 Structure of the Dutch S3-Guidelines on the Treatment of Psoriasis 2011

The Dutch S3-guidelines are divided into different chapters, related to the different treatments of chronic plaque psoriasis, psoriasis of the face and flexures, and childhood psoriasis. A separate chapter provides an overview of the patient's perspective on treatment of psoriasis.

Every chapter starts with the key questions. Subsequently, for each treatment a short introduction is provided, followed by the mechanism of action, dosing regimen, efficacy, adverse effects/safety, contraindications, monitoring, conclusions, considerations, and treatment recommendations. Conclusions are based on current best evidence (Table 1 and 2). The working group members decided to provide conclusions on biologics solely based on grade of evidence A2. Translation of these conclusions into treatment recommendations for daily practice was established by the working group by considering different aspects, such as efficacy, safety, use, availability, and costs of treatment as well as patients' and physicians' preferences. In doing so, the Dutch Society of Dermatology and Venereology hopes to increase transparency of the

Table 1 In- and exclusion criteria for the performed literature search*

Inclusion criteria	Exclusion criteria
Prospective studies (except for psoriasis in children)	Case reports (except for psoriasis in children) and abstracts
Meta-analysis and studies on induction of remission (treatment duration ≤ 16 weeks)	Studies with intralesional or topical administration of systemic treatment (instead of oral administration)
Monotherapy (except for the combination therapies retinoids/phototherapy and topical vitamin D/steroids)	Old-fashioned equipment
Dutch, English, French and German studies	Studies prescribing drugs that are not being used in the Netherlands
Studies with the following parameters: the percentage of patients with nearly complete remission (≥ 90%), the percentage of patients with partial remission (≥ 75%) (and/or duration of remission and/or percentage of improvement of psoriasis measured by PASI, PGA, global severity, body surface area, clearance)	Studies on phototherapy of only parts of the body
Dosing regimen and route of administration have to be stated in studies	Methotrexate dosage > 25 mg/week
Studies with separate data on psoriasis in adults and in children	Acitretin < 0.5 mg/kg/day
Studies with well-described separate data on several clinical subtypes of psoriasis or in case 75% of studied patients have one clinical subtype of psoriasis	Cyclosporine > 5 mg/kg/day
Studies with well-described separate data on levels of severity in patients with psoriasis or in case 75% of studied patients have moderate to severe psoriasis (PASI ≥ 8, topical therapy not sufficient)	

*Note: In case of uncertainty whether a study was performed prospectively the study was excluded. To avoid inaccuracy, data on the percentage of patients with ≥ 90% remission were not extrapolated to the percentage of ≥ 75% remission.

Dutch S3-guidelines. A summary of the considerations of these different aspects is given in this article and can be found within the summary tables for each treatment (see below).

Table 2 Grades of Evidence and Evidence Levels

Grades of Evidence (GE)

A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A1; the results of the different studies included in the meta-analysis must be consistent

A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size)

B Randomized clinical study of lesser quality, or other comparative study (e.g. non-randomized cohort or case-control study)

C Non-comparative study

D Expert opinion

Evidence Levels (EL)

1 One study of level A1 or at least two independently performed studies of level A2

2 At least two independently performed studies of level B

3 One study of level A2 or B or studies of level C

4 Little or no systematic empirical evidence; expert opinions

1.7 Legal consequences of the guidelines

Guidelines are composed in order to guide physicians in providing current, best medical care. The insights on treatment of chronic plaque psoriasis as stated in these guidelines are broadly agreed upon in the Netherlands. However, physicians are not legally required to follow these recommendations. In individual cases it may be desired or may even be necessary to deviate from the recommendations in these guidelines. In doing so, the Dutch physician must argue and document his/her different proceedings and if possible involve the patient in the decision-making.

1.8 Authorization

The full version of the Dutch S3-guidelines on treatment of psoriasis has been authorized by the Dutch Society of Dermatology and Venereology in December 2011. The present summary document has been agreed upon by all members of the working group who wrote chapters for the Dutch version of the S3-guidelines. The working group members approved this summary document.

1.9 Revision of the guidelines

The strength of guidelines lies in their continuous revision. Current medical studies as well as daily practice data and comments by users of these guidelines need to be implemented in future chapters. New chapters will be added to the Dutch S3-guidelines after updating searches on new developments in psoriasis treatment.

Table 3 Choice of treatment

	Efficacy			**Safety**						**Adverse effects**	**Quality of life/ Treatment satisfaction ****	**Costs of therapy and follow-up *****
	≥90 in %	≥75 in %	Duration of remission	Damage to vital organs	Dysfunctions*	Teratogenicity	Carcinogenicity after long-term use	Toxicity in overdose	Drug interactions			
Topical											+	
Calcineurin inhibitors	?	?	+	0	0	?	+	0	0	+		+
Dithranol	30-70%	26-100%	+	0	0	?	0	0	0	+		+/++
Corticosteroids	25-78%	25-89%	+	+	+	0	0	0	0	+		0
Coal tar	?	45-80%	+	0	0	?	?	0	0	0		0
Vitamin D analogues	?	30-50%	+	0	0	?	0	0	0	+		+
Vitamin D/ corticosteroids	?	55-76%	+	+	+	?	0	0	0	+		+
Phototherapy								****			++	
UVB	29-75%	See chapter photother.	++	0	0	0	+	+	0	+		Outpatient: ++ Home: ++
PUVA	79%	See chapter photother.	++	+	+	++/ +++	++	++/ +++	+	++		+++

	Efficacy			Safety						Adverse effects	Quality of life/ Treatment satisfaction **	Costs of therapy and follow-up ***
	≥90 in %	≥75 in %	Duration of remission	Damage to vital organs	Dysfunctions*	Teratogenicity	Carcinogenicity after long-term use	Toxicity in overdose ****	Drug interactions			
Systemic											+++	
Retinoids	11-50%*	25-41%	+/++	+	+/++	+++	0	+/++	+/++	++		+
Methotrexate	11-40%	35-73%	+/++	++	++	++	+	++/+++	++/+++	+/++		+
Cyclosporine	33%	20-71%	+	++/+++	++	+	++	+/++	++/+++	+/++		+/++
Fumaric acid	17-46%	?	++	+/++	+/++	+	0?	+/++	+	++		+
Adalimumab	24-52%	53-80%	++	+	+	+	++	0	+	+		+++
Etanercept	11-21%	30-49%	+	+	+	+	+	0	+	+		+++
Infliximab	41-57%	64-88%	++	+	+	+	++	0	+	++		+++
Ustekinumab	36-51%	66-76%	+++	+	+	+	+	0	+	+		+++

* kidney function disorders, liver function disorders, disorders of fat metabolism +++ more 0 none

** see chapter "The patient's perspective": the groups are judged per group and not per treatment. ++ less ? unclear + least
Phototherapy: UVB outpatient ++, UVB home +++, PUVA +

*** costs reimbursed by insurance company for treatment of 16 weeks

**** explanation (systemic/phototherapy): phototoxicity, nephrotoxicity, hepatotoxicity.

2. Treatment of psoriasis

2.1 Choice of treatment

Deciding which treatment to choose involves the ranking of different criteria. For the topical therapies, phototherapies and systemic monotherapies, the working group ranked the different drugs by different criteria, such as the degree of efficacy, safety, adverse effects, quality of life/treatment satisfaction, costs of therapy, and follow-up. Efficacy is divided into ≥90%, indicating almost complete remission, and ≥ 75%, indicating partial remission. Safety is divided into damage to vital organs, dysfunctions, teratogenicity, carcinogenicity after long-term use, toxicity in overdose, and drug interactions. In table 3, ranking is displayed from +, indicating less common or less serious, to +++, indicating most frequent or most serious. All criteria have been ranked separately for the different psoriatic treatments and cannot be calculated into a total score.

The working group did not value some of the criteria as more important as others. However, patients were able to value criteria in the evaluation of the patient's perspective (Table 3 and chapter 5). The working group holds the opinion that in choosing treatment, the decision has to be made in agreement with the patient and can deviate on individual basis from the norm outlined in these guidelines.

2.2 Topical therapies

P.C.M. van de Kerkhof, R.J. Borgonjen

Table 4 Calcineurin inhibitors

Recommended initial dosage	Tacrolimus (Protopic®) 0.03% ointment, followed by 0.1% ointment 1-2x daily Pimecrolimus (Elidel®) 1% ointment 1-2x daily
Recommended maintenance dosage	Apply until clearance of psoriatic lesions is reached. Then continue regular skin care (i.e., basic treatment, non-medicated ointments)
Important adverse effects (See SmPC)	Burning sensation Folliculitis, viral skin infections.
Prevention/treatment of adverse effects	Stop treatment in case of adverse effects or intolerable burning sensation. Applying topical corticosteroids or disinfectants will rapidly improve symptoms.
Absolute contraindications (See SmPC)	Hypersensitivity to calcineurin inhibitor or any other component of the preparation Primary or secondary immune deficiencies Malignant or premalignant skin lesions Pregnancy and breast feeding

Table 4 Continued

Relative contraindications (See SmPC)	Skin infections (e.g., herpes simplex, folliculitis) UV-light exposure Liver disorder Age <2 years Live vaccines
Important drug interactions	No known drug interactions
Costs	30 g Protopic 0.03% ointment or Elidel cream = €25.79 Protopic 0.1% ointment = €29.04
Special notes	Because of FDA warning: careful when using calcineurin inhibitors combined with phototherapy Due to lack of evidence, do not prescribe calcineurin inhibitors during pregnancy and breast feeding

Conclusions of the Dutch guidelines

EL: 2	Calcineurin inhibitors improve psoriasis compared with placebo if 1) the calcineurin inhibitor is being used under occlusion, 2) the calcineurin inhibitor is combined with a drug that enhances skin penetration (e.g. salicylic acid gel) or 3) the concentration of the calcineurin inhibitor is at least 3 times the registered concentration for atopic dermatitis in the Netherlands. It must be noted that included studies used small patient samples and suffered from substantial drop-outs (18-46%). In a larger study no difference was found between tactrolimus gel, tacrolimus cream and calcipotriol ointment. *A2 Ortonne et al., 2006 (13)* *B Carrol et al., 2005 (14)*

Treatment recommendation

Tacrolimus and pimecrolimus may be used 1-2x daily for chronic plaque type psoriasis in the face, flexures, and anogenital region (see chapter: Treatment of psoriasis of the face and flexures) as an additive (interval treatment) or as a replacement of corticosteroids. Use on other localizations is not recommended.

Be alert to adverse effects, such as burning sensation or irritation of the skin.

Calcineurin inhibitors should not be applied under occlusion or used in combination with UV-therapy.

Dithranol

Table 5 Dithranol

Recommended initial dosage	*Conventional therapy* (hospitalized patients): Initial dosage 0.1% cream or ointment 1x daily, applied on the psoriatic lesions. Do not rinse the preparation. Double concentration, guided by skin irritation, every 3 days until a concentration of 1-3% is reached. In case of extreme skin irritation, consider lowering dosage. Treatment duration: 4-6 weeks; after 2-3 weeks improvement should be noticed. No rebound-effect has been noted when treatment is terminated prematurely. *Short-contact therapy* (non-hospitalized patients): Initial dosage 0.1% cream or ointment applied on the psoriatic lesions, during 10-30 minutes. Rinse the preparation with lukewarm water. Increase the concentration to 1, 2 or 3% based on the amount of skin irritation. Apply during 10-30 minutes. In patients suffering from an irritative response on 0.1%, a concentration of 0.05% should be considered.
Recommended maintenance dosage	Not recommended for long-term therapy
Important adverse effects (See SmPC)	Erythema and burning sensation Discoloration of skin, hair, nails and clothing Blisters and necrosis
Prevention/treatment of adverse effects	When plaques are sharply demarcated the surrounding skin can be protected with zinc paste. Erythema and burning sensation can be treated with topical corticosteroids during 1-2 days. In case dithranol comes in contact with the eyes, this could cause strong irritation or iritis. Rinse the eyes thoroughly with water or prescribe an isotonic saline solution, followed by treatment with topical corticosteroids.
Absolute contraindications (See SmPC)	Erytrodermic psoriasis Pustular psoriasis Psoriatic plaques nearby the eyes or mucosa
Relative contraindications (See SmPC)	Pregnancy (never treat >30% of the skin surface) Children Infants
Important drug interactions	Topical preparations with salicylic acid or urea can enhance the effect of dithranol. Administration of photosensitizing agents in combination with dithranol can enhance the photosensitizing effects.
Costs	€1.83 – €3.92. Additional costs include hospitalization or outpatient treatment.

Table 5 Continued

Special notes	A mild burning sensation indicates effective treatment concentration. Do not apply dithranol on the breasts in breastfeeding women. Patients not experienced with dithranol therapy should receive outpatient or hospitalized treatment.

Conclusions of the Dutch guidelines

EL: 1	The results of the evaluated studies indicate a complete remission (PASI reduction of 100%) in 30-70% of patients and a partial remission (PASI reduction of 75%) in 26-100% of patients after treatment for 5-8 weeks. The differences in efficacy are probably due to the lack of a standardized dithranol treatment strategy and to the differences in clinical settings: home treatment versus outpatient treatment versus hospitalized treatment. Skin irritation, burning sensation, erythema and intermittent brown discolorations are frequently reported adverse effects. Systemic adverse effects have never been reported. *A2 Monastirli et al., 2002 (15); Saraswat et al., 2007 (16)* *B Gerritsen et al., 1998 (17); Prins et al., 2001 (18); Thune et al., 1992 (19); de Mare et al., 1988 (20); Prins et al., 2000 (21); Hutchinson et al., 2000 (22); Mahrle et al., 1990 (23); Swinkels et al., 2002 (24); Van de Kerkhof et al., 2002 (25); Agrup et al., 1985 (26); de Korte et al., 2008 (27); Swinkels et al., 2004 (28); Van de Kerkhof et al., 2006 (29)* *C Agarwal et al., 2002 (30)*

Treatment recommendation

Dithranol monotherapy is recommended in patients with moderate to severe psoriasis for induction therapy during hospitalization or outpatient treatment.

Dithranol short-contact therapy may be an alternative treatment to phototherapy or systemic therapy in patients with moderate to severe psoriasis.

In patients who are unresponsive or have a contraindication to calcipotriol, corticosteroids, photo(chemo)therapy, systemic therapy, and biologics, dithranol is a last resort.

Dithranol therapy should be applied during a maximum of 4-8 weeks. Maintenance or long-term therapy is impractical and has no advantages.

In treating severe chronic plaque type psoriasis, it is recommended to add phototherapy or topical preparations (Vitamin D3 analogues, corticosteroids) to dithranol treatment because of higher efficacy.

Corticosteroids

Table 6 Corticosteroids

Recommended initial dosage	1x daily
Recommended maintenance dosage	Taper when psoriasis improves, for example beta methasone dipropionate 1x daily for 3 weeks, then 1x / 2 days for 1 week, followed by 1x / 3 days for 1 week and then ceasing medication
Important adverse effects (See SmPC)	Skin atrophy, teleangiectasias, secondary infection, rosacea, perioral dermatitis, corticosteroid-induced acne
Prevention/treatment of adverse effects	Adverse effects occurring after long-term treatment include skin atrophy and teleangiectasias. These adverse effects are hard to treat. Try to avoid these adverse effects by taking into consideration therapeutic class of drug, location of drug use and treatment duration. A higher therapeutic class means a higher risk of adverse effects. Long-term treatment with a high potent corticosteroid increases the risk of skin atrophy. The face, genitals, neck and flexures are especially prone to skin atrophy. In the flexures a secondary infection could occur. The face is prone to rosacea, perioral dermatitis and corticosteroid-induced acne. The scalp and the soles of hands and feet can be treated with potent corticosteroids for months or sometimes years before skin atrophy appears.
Absolute contraindications	None
Relative contraindications (See SmPC)	Rosacea, perioral dermatitis Skin infections with bacteria (tuberculosis, lues), fungi, viruses (herpes simplex, herpes zoster, chicken-pox) Adverse effects of vaccines
Important drug interactions	None
Costs	€2.44 daily for topical corticosteroids (10 most prescribed preparations were taken into account) €57.24 per month for mometasone furoate (based on 100g / week)
Special notes	Most patients are afraid to use corticosteroids. Consequently, a detailed advice on benefits and disadvantages needs to be given to patients. During pregnancy, potent corticosteroids may induce intrauterine growth restriction when used on large surfaces for a long time period. During breastfeeding, do not apply corticosteroids on the breasts in order to avoid hospitalization of the infant. The mother must stop breastfeeding in case of long-term treatment with potent corticosteroids.

Conclusions of the Dutch guidelines

EL: 1	After applying high potent corticosteroids (beta methasone dipropionate 2x daily) a substantial improvement or complete remission of skin lesions is seen in 46-56% of patients with psoriasis *A1 Mason et al., 2009 (12)* *A2 Papp et al., 2003 (31); Douglas et al., 2002 (32); Kaufmann et al., 2002 (33)* *B Weston et al., 1988 (34); Bagatell, 1988 (35)*
EL: 1	Therapy with corticosteroids of very high potency (clobetasol-17-propionate 2x daily) has a similar efficacy in 68-89% of patients with psoriasis *A2 Gottlieb et al., 2003 (36); Lowe et al., 2005 (37)* *B Decroix et al., 2004 (38); Lebwohl et al., 2002 (39); Weston et al., 1988 (34); Lee et al., 2009 (40)* *C Mazzotta et al., 2007 (41)*
EL: 2	Due to the small number of available studies and varying study-outcome it is unclear whether clobetasol-17-propionate is more effective as a cream, lotion, spray or foam. *A2 Lowe et al., 2005 (37)* *B Lebwohl et al., 2002 (39); Lee et al., 2009 (40)* *C Mazotta et al., 2007 (41)*
EL: 2	Owing to the small number of available studies it is unclear whether 1x daily application of topical corticosteroids is more effective than 2x daily application. *A2 Kaufmann et al., 2002 (33)*

Treatment recommendation

Topical corticosteroids are recommended for the treatment of mild to severe chronic plaque psoriasis. Combination therapy with calcipotriol, phototherapy, or systemic therapy may be prescribed, thereby reducing the total dosage of corticosteroids significantly.

The class of corticosteroids prescribed depends upon the areas of skin affected.

It is important to be aware of the occurrence of skin atrophy or teleangiectasia, especially when corticosteroids are used as long-term therapy and are being applied in areas prone to these adverse effects.

Owing to lack of evidence for 2x daily application of corticosteroids over 1x daily application, it is recommended to start with 1x daily.

Coal tar

Table 7 Coal tar

Recommended initial dosage	No recommended initial dosage; the dosage of coal tar may vary
Recommended maintenance dosage	It is not recommended to use coal tar for maintenance or long-term therapy
Important adverse effects (See SmPC)	Coal tar odor, staining,phototoxicity
Prevention/treatment of adverse effects	The brown-black stains in clothing and the penetrating odor are unavoidable. Patients should exercise caution with exposure to sunlight in order to avoid UV-erythema.
Absolute contraindications (See SmPC)	Pregnancy and breastfeeding Xeroderma pigmentosum, dysplastic nevus syndrome, basal cell nevus syndrome
Relative contraindications (See SmPC)	Intense exposure to sunlight or UV-light during treatment Prior history of skin cancer
Important drug interactions	There are no drug interactions reported for topical use of coal tar products
Costs	€3.51 daily
Special notes	The Goeckerman-method consists of application of coal tar during 1-2 hours followed by UVB therapy. Optimal dosage of UVB is reached when the treated skin does not become erythematous. In outpatient care, pix lithantracis is often used and in combination with UV-therapy shows a higher efficacy when compared with liquor carbonis detergens (LCD)/UV-light combination therapy.

Conclusions of the Dutch guidelines

EL: 3	Coal tar monotherapy (10% LCD) seems to improve psoriatic lesions when compared with placebo, but is less effective than betamethasone valerate. *B Thawornchaisit et al., 2007 (42)*

EL: 2	Coal tar (5%) is being used in clinical studies combined with phototherapy. When combined with UV-light a reduction of 75% in PASI score (PASI 75) was reached in 45-80% of participants after 15-20 applications. The evidence on the additive effect of coal tar when combined with phototherapy is insufficient. The addition of coal tar might result in a faster and longer remission. *B Bagel, 2009 (43); Belsito et al., 1982 (44)* *C Frost et al., 1979 (45)*

Treatment recommendation

Coal tar is not the first-choice of treatment for chronic plaque psoriasis.
Coal tar as a monotherapy is outdated. Nowadays, treatment options exist that are less hazardous and more practical.
Only when therapeutically necessary, coal tar or pix lithanthracis may be used in combination with UVB or PUVA to treat recalcitrant chronic plaque psoriasis.

Tazarotene

Tazarotene is not available in the Netherlands and therefore not included in these guidelines.

Vitamin D3 analogues

Table 8 Vitamin D3 analogues

Recommended initial dosage	Calcipotriol: 2x daily on affected areas of the skin Calcitriol: 2x daily on affected areas Calcipotriol/betamethasone: 1x daily on affected areas
Recommended maintenance dosage	Calcipotriol: ≤15g cream or ointment daily and ≤100g weekly Calcitriol: ≤30g ointment daily and ≤35% of body surface area Calcipotriol/betamethasone: continuous use during 4 weeks. Owing to lack of evidence on long-term continuous therapy, intermittent use of this drug is recommended
Important adverse effects (See SmPC)	Burning sensation, redness Overdosing: hypercalcemia, bone resorption, possibly uric acid kidney stones, or even kidney failure
Prevention/treatment of adverse effects	Do not treat unaffected skin areas. In case of skin irritation, adjust frequency of therapy or stop briefly. Topical corticosteroids may reduce irritation.
Absolute contraindications	None
Relative contraindications (See SmPC)	Pustular psoriasis Diseases involving disorders of calcium metabolism Treatment with medication that can cause hypercalcemia Serious kidney or liver disease Due to lack of experience, treatment during pregnancy and breastfeeding should be avoided
Important drug interactions	Topical salicylic acid (inactivation), avoid other topical irritating preparations Oral calcium supplementation, oral vitamin D3, thiazide diuretics: check serum calcium levels
Costs	120g calcipotriol cream: €37.26 100g calcitriol ointment: €23.70 100g Dovobet (calcipotriol/betamethasone): €68,-

Table 8 Continued

Special notes	Do not apply calcipotriol before treatment with UV-light. It can diminish the effect of UV-therapy. Calcipotriol may be administered after phototherapy.

Conclusions of the Dutch guidelines

EL: 1	After topical application of vitamin D3 analogues 30-50% of patients with mild to moderate chronic plaque psoriasis improved substantially or even achieved almost complete remission within several weeks *A2 Camarasa et al., 2003 (46); Kragballe et al., 2004 (47); Zhu et al., 2007 (48); Guenther et al., 2000 (49)*

EL: 1	Efficacy and tolerance of vitamin D3 analogues are enhanced by combining therapy with topical corticosteroids during the first phase of treatment. Usage of calcipotriol/betamethasone dipropionate ointment or gel is preferred because of a higher patient compliance with 1x daily application *A2 Papp et al., 2003 (31); Douglas et al., 2002 (32); Kaufmann et al., 2002 (33); Tabolli et al., 2009 (50); Guenther et al., 2002 (51); Kragballe et al., 2004 (47); Ortonne et al., 2004 (52); Kragballe et al., 2006 (53); Peeters et al., 2005 (54); Saraceno et al., 2007 (55)*

Treatment recommendation

Vitamin D3 analogues are recommended as topical therapy for chronic plaque psoriasis. Efficacy and tolerance is higher for the combination of vitamin D analogues with corticosteroids when compared with both monotherapies. The combination preparation is preferred because of its 1x daily application.

For treatment of moderate to severe chronic plaque psoriasis the use of topical vitamin D3 analogues combined with UV-therapy or systemic therapy is recommended.

2.3 Phototherapy

E.P. Prens, W.J.A. de Kort, M.B.G. Koek

Table 9 Phototherapy

Registration for psoriasis	More than 50 years of experience with the oldest modality (Goeckerman)
Recommended control parameters before starting treatment	Regular inspection of skin every 8 to 10 treatments. Ask for UV-erythema.
Recommended initial dosage	Individual dosage depends on skin type; follow one treatment regimen until erythema occurs, then: UVB: 70% of the minimal erythema dosage (MED) Oral PUVA: 75% of the minimal phototoxic dosage (MPD) Bath/cream PUVA: 30-50% of MPD
Recommended maintenance dosage	Increase dosage (10-30%) based on erythema
Onset of effect	After 2-3 weeks
Response rate	UVB: 75% of patients a PASI 75 after 4-6 weeks (EL: 2) PUVA: complete clearance of skin lesions in 75-90% of patients (EL: 2)
Absolute contraindications	Photodermatoses/photosensitivity, skin malignancies, treatment with cyclosporine (immunosuppressant) and expected treatment with cyclosporine in future. PUVA: pregnancy or lactation. This is a relative contraindication for bath PUVA.
Relative contraindications	Epilepsy, pregnancy or lactation (for bath PUVA), unavoidable therapy with photosensitizing agents, skin type I, dysplastic melanocytic nevi, prior history of skin cancer, poor compliance, physical or emotional inability to sustain therapy (heart failure NYHA class III-IV, claustrophobia), presence of actinic skin damage, children < 18 years, high cumulative number of treatments or dosage (for UVB: 400 treatments, this equals approximately 600-800 J/cm^2 for narrow band UVB and 120-180 J/cm^2 for broadband UVB therapy). For oral PUVA: High cumulative number of treatments (1000 J/cm^2 or 150-200 treatments), prior arsenic treatment or ionizing radiation, significant liver damage.
Most common adverse effects	≥1/10: Erythema, itch, hyperpigmentation. Only for PUVA: nausea. Only for excimer laser: blistering.
Important drug interactions	Note: medication capable of inducing phototoxicity or photoallergy.
Special notes	Combination with topical preparations may work synergistically. PUVA should not be combined with cyclosporine. Eyes must be protected during phototherapy, as well as the penis and scrotum.

Table 10 Important adverse effects of UVB and PUVA therapy

Most frequently	Erythema, itch, hyperpigmentation Only PUVA: nausea Only excimer laser: blistering
Frequently	-
Sometimes	Blistering
Rarely	Oral PUVA: squamous cell carcinoma, basal cell carcinoma
Very rarely	-

Table 11 List of medication capable of inducing phototoxicity and photoallergy

Drugs inducing phototoxicity	**Drugs inducing photoallergy**
Tetracyclines	Tiaprofenic acid
Phenothiazine	Promethazine
Griseofulvin	Chlorpromazine
Nalidixine acid	Hydrochlorothiazide
Furosemide	Quinine
Amiodarone	Para-aminobenzoic acid (PABA) ointments
Piroxicam	Desinfectants (hexachlorophene, others)
Tiaprofenic acid	

Table 12 Starting dosage UVB therapy (56)

Skin type	**UVB broadband** (mJ/cm^2)	**Narrow band UVB** (mJ/cm^2)
I	20	200
II	30	300
III	50	500
IV	60	600

Table 13 Treatment regimen UVB phototherapy (56)

Step 1 Assessment of MED	Assess after 24 hours	
Step 2 Start of therapy	Starting dosage	According to skin type or 70% of MED
Step 3 Treatment 2-3 times per week	No erythema	Increase by 30%
	Minimal erythema	Increase by 20%
	Persisting asymptomatic erythema	Do not increase dosage
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Lower last dosage by 50% Increase further by 10%

Table 14 Treatment regimen localized UVB phototherapy (excimer laser or lamp) (57)

Step 1 Assessment of MED	Assess after 24 hours	
Step 2 Start of therapy	Starting dosage	2x-4x of MED
Step 3 Treatment 2 times per week	Persisting asymptomatic erythema	Increase with 1x-2x MED
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Repeat last dosage

Table 15 PUVA: most commonly used photosensitizing agents and their dosage (56, 58)

Modality	Photosensitizing agent	Dosage or concentration
Oral PUVA	8-methoxypsoralen (8-MOP) 5-methoxypsoralen (5-MOP)	0.6 mg/kg 1.2 mg/kg
Bath PUVA	8-MOP	0.5-5.0 mg/L
localized PUVA (emulsion or gel)	8-MOP	1%-0.005%

Table 16 PUVA starting dosages (57)

Skin type	Oral PUVA		Bath PUVA
	8-MOP (J/cm^2)	**5-MOP** (J/cm^2)	**1.0 mg/L 8-MOP** (J/cm^2)
I	0.3	0.4	0.2
II	0.5	1.0	0.3
III	0.8	1.5	0.4
IV	1.0	2.0	0.6

Table 17 PUVA treatment regimen (57)

Step 1 Assessment of minimal phototoxic dosage	Oral PUVA: assess after 72-96 h Bath PUVA: assess after 72-96 h	
Step 2 Start of therapy	Starting dosage	Oral PUVA: According to skin type or 75% of MPD Bath PUVA: According to skin type or 30-50% of MPD
Step 3 Treatment 2x per week	No erythema, good response	Increase by 30% (max. 2 times per week)
	Minimal erythema	Do not increase
	Persisting asymptomatic erythema	Do not increase
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Lower last dosage by 50%; increase further by 10%

Conclusions of the Dutch guidelines

UVB (broadband)

EL: 2	About 75% of all patients treated with broadband UVB 2-3 times per week achieved at least PASI 75 response after 4-12 weeks (depending on UV schedule) and clearance was reached in most cases. *A2 Dover et al., 1989 (59)* *B Coven et al., 1997 (60); Orfanos et al., 1979 (61); Petrozzi, 1983 (62); Ramsay et al., 2000 (63)*

UVB (narrow band)

EL: 2	63% - >75% of all patients treated with narrow band UVB 2-3 times per week reached at least PASI 90 response within 20 weeks of treatment. Presumably higher response percentages are achieved for PASI 75. Exact data are not available since performed studies date before the "PASI-era". *B Arnold et al., 2001 (64); Gordon et al., 1999 (65); Markham et al, 2003 (66); Youssef et al., 2008 (67)*

EL: 2	It is unclear whether phototherapy > 3 times per week results in a higher efficacy and faster response. *B Coven et al., 1997 (60); Grundmann-Kollmann et al., 2004 (68); Leenutaphong et al., 2000 (69)*

EL: 2	The percentage of patients achieving PASI 75, PASI 90 or complete clearance is equally high for home UVB phototherapy as for outpatient phototherapy. *A2 Koek et al., 2009 (70)* *B Cameron, 2002 (71)*

EL: 2	No significant difference exists between home and outpatient phototherapy for total cumulative dosage of UVB at the end of treatment. There is also no difference between both therapies for percentage of adverse effects as for the number of adverse effects experienced at least once by patients with psoriasis. *A2 Koek et al., 2009 (70)* *B Cameron, 2002 (71)*

UVB 308 nm

EL: 2	Individual plaques disappear completely (in 33-37%) or almost completely (about 70%) after treatment with the excimer laser for 8-16 weeks. *B Hacker et al., 1992 (72); Taibjee et al., 2005 (73); Trehan et al., 2002 (74); Goldinger et al., 2006 (75)* *C Feldman et al., 2002 (76); Han, 2008 (77)*

EL: 3	There is evidence the results of the excimer lamp equal the excimer laser. *B Kollner et al., 2005 (78)*

Oral PUVA

EL: 2	After 12-16 weeks, 75-90% of patients achieve near complete clearance of skin lesions when treated with oral PUVA 2-4 times per week *A2 Yones et al., 2006 (79)* *B Caca-Biljanovska et al., 2002 (80); Barth et al., 1978 (81); Berg et al., 1994 (82); Buckley et al., 1995 (83); Calzavara-Pinton et al., 1992 (84); Collins et al., 1992 (85); Cooper et al., 2000 (86); Diette et al., 1984 (87); Hanke et al., 1979 (88); Khurshid et al., 2000 (89); Kirby et al., 1999 (90); Park et al., 1988 (91); Parker et al., 1984 (92); Parrish et al., 1974 (93); Rogers et al., 1979 (94); Vella Briffa et al., 1978 (95); El-Mofty et al., 2008 (96)* *C Henseler et al., 1981 (97)*

Bath PUVA

EL: 2	The results of bath PUVA equal oral PUVA when treatment frequencies are similar. *B Caca-Biljanovska et al., 2002 (80); Barth et al., 1978 (81); Berg et al., 1994 (82); Buckley et al., 1995 (83); Calzavara-Pinton et al., 1992 (84); Collins et al., 1992 (85); Cooper et al., 2000 (86); Diette et al., 1984 (87); Hanke et al., 1979 (88); Khurshid et al., 2000 (89); Kirby et al., 1999 (90); Park et al., 1988 (91); Parker et al., 1984 (92); Parrish et al., 1974 (93); Rogers et al., 1979 (94); Vella Briffa et al., 1978 (95); El-Mofty et al., 2008 (96)*

Retonoid plus PUVA / UVB

EL: 2	There is evidence that combination therapy with PUVA / acitretin or narrow band UVB / acitretin achieves higher efficacy and is dose-sparing in regard to cumulative UV dosage. *B Saurat et al., 1988 (98); Carlin et al., 2003 (99); Lauharanta et al., 1989 (100)*

Instructions for phototherapy

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination need to be directed at prior exposure, melanocytic nevi (in particular dysplastic type) and skin cancer
- Additional UV exposure due to recreational activities should be taken into account
- Prescription of UVA protecting sunglasses is obligatory before commencing oral PUVA therapy
-

During treatment
- Physical examination
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- UV dosages should be documented with precise cumulative units (J/cm^2 or mJ/cm^2) and number of treatments

- Ask for the occurrence of erythema on a regular basis in order to accurately determine treatment dosage
- Physicians should report adverse effects, therapeutic response and concomitant treatments within the medical record
- Eyes should always be protected during phototherapy with sunglasses with UV-protection as well as at least 8 hours after oral-PUVA treatment
- Cover the genital area when skin lesions are absent. If desired, healthy skin of the face and other unaffected areas may be covered (possibly with adequate sunscreens). The area of covered skin needs to be the same during every treatment since a shift of 1 cm may cause burns due to unequal sensitivity of this area to UV light
- It is essential for the patient to avoid additional sun exposure and/or to use sunscreens

After treatment

- After a treatment course, cumulative UV-dosage and number of treatments should be registered
- Especially patients with high number of treatment episodes (200-250x PUVA) need to be screened routinely for skin cancer during their entire life

Treatment recommendation

Phototherapy is recommended for induction therapy of moderate to severe chronic plaque psoriasis. Narrow band UVB is recommended as first choice; PUVA is advised in case UVB is ineffective.

8-MOP or methoxsalen is preferred for PUVA therapy. This preparation, however, is being withdrawn from the market. The manufacturer states Oxsoralen (methoxsalen 10 mg capsules) can be imported by the pharmacist with a delivery time of a week. Oxsoralen is not registered in the Netherlands and will not be reimbursed. The dermatologist should contact the health insurance of the patient to arrange a reimbursement for a non-registered drug.

The use of excimer lasers should be limited to treatment directed at single, therapy resistant psoriatic plaques.

UV maintenance therapy is not recommended owing to decreased efficacy after repetitive UV-exposure and increased chance of UV skin damage. The number of treatment courses should be limited to a maximum of 2 per year.

UV-therapy after or during immunosuppressant drugs, especially cyclosporine, demands special attention.

Both home and outpatient UVB phototherapy are available for the treatment of psoriasis. The dermatologist should, in consultation with the patient, decide which treatment setting is preferred.

2.4 Conventional systemic therapies

Methotrexate

E.M.G.J. de Jong

Table 18 Methotrexate

Registration for psoriasis	1958
Recommended control parameters before starting treatment	Hb, leucocytes and differential, thrombocytes, liver enzymes, serum creatinine, urine sediment, pregnancy test, HBV/HCV, serum albumin, PIIINP if available, X-thorax in case of suspected tuberculosis on anamnesis.
Recommended initial dosage	5-10 mg weekly
Recommended maintenance dosage	5-22.5 mg weekly (oral, subcutaneous or intramuscular)
Onset of effect	After 4-12 weeks
Response rate	PASI 75 in 35-73% of patients after 16 weeks
Absolute contraindications (See SmPC)	Severe infections, serious kidney and liver diseases, bone marrow diseases, substantial hematologic abnormalities, men and women planning to have children, pregnancy, breastfeeding, pulmonary fibrosis or poor lung function, alcohol abuse, immune deficiencies, acute peptic ulcer, drug abuse.
Relative contraindications (See SmPC)	High age, less serious kidney and liver diseases, ulcerative colitis, history of HBV or HCV, poor compliance, gastritis, diabetes, history of malignancies, heart failure, drug interactions
Most common adverse effects (See SmPC)	≥1/10: stomatitis, dyspepsia, nausea, loose of appetite. Increase of serum transaminases. ≥1/100 - ≤1/10: oral ulcers, diarrhea. Exanthema, erythema, itch. Headache, fatigue, sleepiness. Interstitial alveolitis or pneumonitis: symptoms of potentially severe damage are dry, unproductive cough, dyspnoe and fever. Leukopenia, anemia, trombopenia.
Important drug interactions	Trimethoprim, probenecide, retinoids, NSAIDs

Table 18 Continued

Special notes	Dosing once a week; overdose may lead to leukocytopenia or pancytopenia which may be life-threatening. Continue oral contraceptives until 3 months after cessation of MTX. Alcohol consumption, obesity, hepatitis and diabetes increase the risk of hepatotoxicity. In geriatric patients a lower dose of MTX is usually prescribed and kidney function should be monitored on a regular basis.

Conclusions of the Dutch guidelines

EL: 1	Methotrexate is effective for the treatment of plaque psoriasis in adults. After 16 weeks, in 35-73% of patients with psoriasis a PASI 75 response was reached on 15-22.5mg methotrexate weekly. *A2 Flystrom et al., 2008 (101); Ranjan et al., 2007 (102); Saurat et al., 2008 (103); Heydendael et al., 2003 (104); Akhyani et al., 2010 (105)*

Table 19 Important adverse effects of MTX

Most frequently	Stomatitis, dyspepsia, nausea, loose of appetite. Increase of serum transaminases. Hair loss.
Frequently	Oral ulcers, diarrhea. Leukopenia, anemia, trombopenia.
Sometimes	Fever, shivers, depression, infections
Rarely	Nephrotoxicity, liver fibrosis / cirrhosis
Very rarely	MTX alveolitis or pneumonitis.

Table 20 List of medication and drug interactions

Medicine	Type of drug interaction
Colchicin, cyclosporine, NSAIDs, penicillin, probenecide, salicylic acids, sulfonamides	Reduced renal clearance of MTX
Chloramphenicol, co-trimoxazol, cytostatics, ethanol, NSAIDs, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazol, phenytoin, probenecide, NSAIDs, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased risk of hepatotoxicity

Instructions for MTX use

Prior to treatment
- Medical history and physical examination
- Assessing disease severity, preferably with PASI or PGA
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Laboratory controls (Table 21)
- Start contraceptives in fertile women (start after menstruation), contraceptive measures in men
- In case liver function screening shows abnormalities, refer to specialist for further evaluation
- Influenza vaccination is recommended
- X-thorax in case of suspected tuberculosis on anamnesis.

During treatment
- Objective assessment of disease severity using PASI or PGA
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history
- Physical examination
- Laboratory controls (Table 21)
- Contraceptive measures in fertile women and men
- Administer folic acid once weekly at least 24 hours after MTX*
- Intake of MTX with milk reduces the absorption of MTX

After treatment
- Women should not become pregnant and men should not conceive children during MTX treatment and 3 months thereafter.

* Folic acid dosage varies in the literature between 1 to 5mg daily and 1 to 2.5-10mg weekly (Prey, 2009). *The working group of these guidelines holds the opinion that dosage of folic acid should be flexible with 1mg daily (except for the day of MTX intake) to 5-10mg once weekly administered at least 24 hours after MTX intake. The guidelines of the Dutch Society of Rheumatology advice to prescribe at least 5mg of folic acid weekly, at least 24 hours after MTX intake. It is recommended to double this dosage in case MTX dosage becomes ≥15mg weekly.*

Table 21 Laboratory controls

Parameter*	Prior to treatment	After the first week of treatment	During the first two months 1x every 2 weeks, thereafter every 2-3 months.
Hb, leucocytes and differential, thrombocytes, erythrocytes	X	X	X
Liver enzymes (ALAT, AP, yGT)	X	X	X
Serum creatinine	X	X	X
Urine sediment	X	X	X
Pregnancy test	X		
HBV/HCV	X		
Serum albumin**	X	X	X
PIIINP if available	X	Every 3 months***	

Further testing may be required based on patient's status, risk and exposures.

* Decrease MTX dosage or stop MTX in case leukocytes are <3.0, neutrophils <1.0, thrombocytes<100 or liver enzymes >2x the upper limit normal range

** In certain patients (e.g. suspicion of hypoalbuminemia or patients using other medication with strong serum albumin binding properties)

*** Liver biopsy should be considered in selected patients, e.g. patients with a continuous elevated PIIINP level (>4.2 mcg/l in at least 3 samples during a 12 month time period)

Table 22 PIIINP (amino-terminal propeptide of type III pro-collagen) cut-off levels and clinical guidance

PIIINP (amino-terminal propeptide of type III pro-collagen) for psoriasis
Reference range: 1.7 – 4.2 mcg/L. First serum sample before starting MTX, thereafter 1x every 3 months. Confounding factors: arthritis, age <18 years, scleroderma, myeloproliferative disorders, malignancies (breast carcinoma, hepatocellular carcinoma, ovarian carcinoma), recent myocardial infarction.
A gastroenterologist should be consulted (after exclusion of confounding factors) when: PIIINP value is >8.0 mcg/L prior to starting MTX PIIINP value is >4.2 mcg/L in at least 3 samples during a 12 month time period PIIINP value is >8.0 mcg/L in at least 2 consecutive samples PIIINP value is >10 mcg/L in 1 sample. In this case, provisionally stop MTX.

Table 23 Liver biopsy: Roenigk classification of liver damage and its therapeutic consequences

Histological classification:
Grade I: Normal
Grade II: Changes, no fibrosis
Grade IIIA: Mild fibrosis
Grade IIIB: Moderate to severe fibrosis
Grade IV: Cirrhosis
Therapeutic consequences:
Grade I and II: MTX may be continued
Grade IIIA: MTX may be continued, but liver biopsy needs to be repeated after 6 months
Grade IIIB and IV: stop MTX

Table 24 Folic acid dosage in case of MTX overdose

Serum MTX (M)	**Parenteral administration of folic acid once every 6 hours (dosage in mg)**
5 x 10-7	20
1 x 10-6	100
2 x 10-6	200
>2 x 10-6	Increase dosage proportionally

Treatment recommendation

Treatment with methotrexate (15-22.5 mg/week) is effective for plaque psoriasis and induces a reduction of PASI score of at least 75% (PASI75) in 35-73% of patients after 16 weeks of treatment. Owing to its slow onset of effect, methotrexate is less suitable for short induction treatment than for long-term therapy.

It is recommended to supply folic acid to reduce the risk of hepatic adverse effects. The dosage may vary from 1mg daily (except for the first day of MTX intake) to 5-10mg once weekly, with a time interval between MTX intake and start of folic acid of at least 24 hours.

Before starting MTX therapy and every 3 months thereafter, it is recommended to monitor for liver damage by measuring liver enzymes and PIIINP.

PIIINP measurement should be available for all Dutch dermatologists. Values should be given preferably with interpretation of the results and advice. Several hospitals

should offer the possibility of PIIINP measurement. Currently, PIIINP measurement is available in the University Medical Centre Nijmegen and VU Medical Centre Amsterdam.
Because of the occurrence of overdosing of MTX (e.g. prescribed once daily instead of once weekly) with sometimes lethal consequences it is recommended to prescribe the recipe for MTX carefully. It must be clearly stated that dosage is once weekly. It is strongly advised by The Dutch health inspection that physicians should state the indication of MTX on the recipe. Patients should be informed about the once weekly treatment regimen.
Owing to the possible mutagenic effects of MTX fertile men and woman should be strongly advised to use reliable contraceptives.

Cyclosporine

Ph.I. Spuls, M. de Groot

Table 25 Cyclosporine

Registration for psoriasis	1993
Recommended control parameters before starting treatment	Hb, leucocytes and differential, thrombocytes, serum creatinine, urea, uric acid, liver enzymes (ASAT, ALAT), bilirubin, alkaline phosphatase, yGT, LDH, albumin, sodium, potassium, magnesium only in case of muscle cramps, urine sediment, cholesterol / triglycerides, pregnancy test, blood pressure.
Recommended initial dosage	2.5-3 (max. 5) mg/kg per day for 4-6 weeks. When skin does not improves, increase to 5 mg/kg/day
Recommended maintenance dosage	Lower dosage every two weeks until a maintenance dosage of 0.5-3 mg/kg/day is reached, divided into 2 doses. Increase dosage in case of recurrence of psoriasis. Maximal total duration of therapy: 2 years. (EDF guidelines, 2009)
Onset of effect	After 4 weeks
Response rate	The response is dose-dependent. After 8-16 weeks of treatment with 3 mg/kg/day, PASI 75 is reached in approximately 50% of patients after 8 weeks.
Absolute contraindications (See SmPC)	History of serious adverse effects on or hypersensitivity to cyclosporine, poor kidney function, severe liver disease, severe hypertension, serious infections, malignancy (current or past, especially hematologic or cutaneous malignancies except for basal cell carcinoma), concurrent PUVA treatment, contra-indicated concomitant medication, vaccination with live vaccines, gout.

Table 25 Continued

Relative contraindications (See SmPC)	Prior potential carcinogenic treatment (arsenic, PUVA > 1000 J/cm^2 or 150-200 applications), prior long-term MTX use, psoriasis induced by serious infection or medication (beta blocker, lithium, antimalarial medication), liver function disorders, hyperuricemia, hyperkalemia, epilepsy/ convulsions, inadequate efficacy in the past, simultaneous treatment with nephrotoxic drugs, polypharmacy (e.g., HIV patients), simultaneous use of other systemic immunosuppressive drugs, concurrent phototherapy, simultaneous use of systemic retinoids or retinoid therapy 4 weeks prior to commencing cyclosporine treatment, drug or alcohol related diseases or substance abuse or alcohol abuses, pregnancy/breastfeeding, current treatment with ricinus oil preparations.
Most common adverse effects (See SmPC)	≥1/100 - <1/10: kidney insufficiency (dose-dependent), irreversible kidney damage (long-term therapy), hypertension, gingival hyperplasia, reversible gastrointestinal complaints (dose-dependent), tremor, fatigue, headache, burning sensation of hands and feet, reversible hyperlipidemia (especially in combination with systemic corticosteroids), hypertrichosis, abnormal liver function tests.
Important drug interactions	Many different drug interactions: see SmPC text and Dutch guidelines (http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
Special notes	Increased risk of lymphoproliferative diseases in transplant patients. Increased risk of squamous cell carcinoma in patients with psoriasis after photo(chemo)therapy (106). *Special warnings:* - The capsules contain a small amount of alcohol (intake of 100 mg capsules equals 0.1 g alcohol) - There is a potential risk of drug interactions, especially with statins (increased risk of myopathy). - When idiopathic intracranial hypertension is diagnosed, cyclosporine should be stopped in order to avoid permanent decline in vision. - Yearly assessment of GFR is the most accurate method in order to assess kidney tolerance to cyclosporine in long-term therapy. - Supplementation with magnesium seems to protect against loss of kidney function as well as chronic cyclosporine nephrotoxicity by adapting the activity of nitrogen monoxide synthase (107).

Table 25 Continued

Special notes	*Special attention to switching therapies:* - Switching from cyclosporine to other cyclosporine (other manufacturer): be aware of differences in biological availability and if necessary adjust dosage. - Cyclosporine may be used after systemic retinoid therapy, that is 4 weeks after cessation of retinoid treatment. - Fumaric acid esters and cyclosporine are usually not combined. - In case of insufficient response to cyclosporine a switch to a biological agent may be considered. A period of simultaneous usage of both biological agent and cyclosporine may be considered in spite of synergistic toxicity (infections, hepatotoxicity).

Conclusions of the Dutch guidelines

EL: 1	Cyclosporine is effective for the treatment of moderate to severe chronic plaque psoriasis in adults. PASI 75 was reached in 20-71% of patients with psoriasis on 2.5-5 mg/kg/day cyclosporine at week 8-16 and PASI 90 was reached in 33% of patients on 3-5 mg/kg/day at week 16. Most included studies showed a clinical relevant response 4-6 weeks after commencing therapy. *A2 Heydendael et al., 2003 (104); Gisondi et al., 2008 (108); Koo, 1998 (109); Ellis et al., 1991 (110)*

Table 26 Important adverse effects of cyclosporine

Frequently	Kidney insufficiency (dose-dependent), irreversible kidney damage (long-term therapy), hypertension, gingival hyperplasia, reversible gastrointestinal complaints (dose-dependent), tremor, fatigue, headache, burning sensation of hands and feet, reversible hyperlipidemia (especially in combination with systemic corticosteroids), hypertrichosis, abnormal liver function tests.
Sometimes	Convulsion, gastrointestinal ulcers, weight gain, hyperglycemia, hyperuricemia, hyperkalemia, hypomagnesemia, acne, anemia.
Rarely	Ischemic heart disease, pancreatitis, polyneuropathy (motoric), decreased eyesight, decreased hearing, central ataxia, myopathy, erythema, itch, leucopenia, thrombocytopenia.

Table 26 Important adverse effects of cyclosporine

Very rarely	Microangiopathic hemolytic anemia, hemolytic uremic syndrome, colitis (isolated cases), papillary oedema (isolated cases), idiopathic intracranial hypertension (isolated cases).

Instructions for cyclosporine use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination need to be directed at prior diseases and current comorbidity (e.g., serious infections, (skin) malignancies, kidney and liver diseases). Also, possible drug-interactions involving current concomitant medication and contraindications should be ruled out
- Measure blood pressure at two separate consultations if first measurement was elevated
- Laboratory controls (Table 27)
- Reliable contraceptive (note: contraceptives with progesterone become less effective)
- Gynecological screenings should be performed on a regular basis according to the Dutch national guidelines on cervix carcinoma
- Inform patients about vaccination (especially live attenuated vaccines), patient's susceptibility to infections (take infections serious, apply adequate medical assistance), drug interactions (inform other treating physicians on therapy), avoidance of excessive sun exposure, advice the use of sunscreens

During treatment
- Objective assessment of disease severity (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should include examination of skin and mucous membranes for formation of skin malignancies (also inspect for increase of hair growth on the body, gingival changes), signs of infections, gastrointestinal or neurological symptoms
- Repeat the advice on avoidance of excessive sun exposure and using sunscreens
- Check concomitant medication
- Measure blood pressure
- Laboratory controls (Table 27)
- If creatinine levels are increased or if patient is treated $>$ 1 year, assess the creatinine clearance (or 51 Cr-labeled EDTA clearance if available)
- Routine assessment of cyclosporine serum levels is not recommended (see Dutch S3-guidelines for details: http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
- Reliable contraceptive

After treatment
- After cessation of cyclosporine, the dermatologist needs to inspect the patient for the formation of skin malignancies, especially in cases in which extensive UV-therapy or UV-exposure preceded cyclosporine treatment.

Table 27 Laboratory controls

Parameter	Prior to treatment	Treatment period (in weeks)				
		2	4	8	12	16
Blood count*	X	X	X	X	X	X
Liver values**	X	X	X	X	X	X
Electrolytes***	X	X	X	X	X	X
Serum creatinine	X	X	X	X	X	X
Urine sediment	X		X			X
Urea and uric acid	X		X	X	X	X
Pregnancy test (urine)	X					
Cholesterol, triglycerides	X****			X		X
Magnesium*****	X			X		X

* Leucocytes, thrombocytes, erythrocytes
** Transaminase, AP, yGT, bilirubin, LDH, albumin
*** Sodium, potassium
**** Recommended 2 weeks prior to treatment and on the first day of treatment (fasting).
***** Only if indicated (e.g., muscle cramps). Also consider CPK.

Treatment recommendation

3-5 mg/kg/day Cyclosporine is recommended for induction therapy in patients with moderate to severe plaque psoriasis. Because of its fast onset of action, cyclosporine is appropriate for short-term induction therapy or crisis intervention.
Cyclosporine may be used to induce remission in adults with moderate to severe chronic plaque psoriasis who are undertreated with topical preparations or phototherapy.
Cyclosporine may be used for long-term treatment (up to 2 years) in individual cases, but patients must be screened intensively for signs of toxicity, especially for decrease in kidney function and the development of hypertension.

Retinoids

M. te Booij, P.C.M. van de Kerkhof, M.C. Pasch

Table 28 Retinoids

Registration for psoriasis	1992 (Germany)
Recommended control parameters before starting treatment	Hb, Hct, leukocytes, trombocytes, liver enzymes (ASAT, ALAT), AP, yGT, serum creatinine, pregnancy test, blood glucose (fasting), triglycerides/cholesterol/HDL, perform X-ray examination of bones when symptoms exist (Ormerod, 2010)
Recommended initial dosage	0.3-0.5 mg/kg/day during 4 weeks, followed by 0.5-0.8 mg/kg/day
Recommended maintenance dosage	Individual dosage depends on response and tolerance
Onset of effect	After 4-8 weeks
Response rate	Varies strongly and is dose-dependent, unambiguous conclusions cannot be stated, 25-75% reach partial remission (PASI 75) (30-40 mg/day) (Level of evidence: 3)
Absolute contraindications (See SmPC)	Kidney and liver damage, fertile women planning to have children, concomitant medication interacting with retinoids, hepatotoxic concomitant medication, pregnancy, breast-feeding, alcohol abuse, blood donation.
Relative contraindications (See SmPC)	Alcohol use (111), diabetes mellitus, use of contact lenses, children, history of pancreatitis, hyperlipidemia (especially hypertrygliceridemia) and hyperlipidemia treated with medication, atheroclerosis.
Most common adverse effects (See SmPC)	≥ 1/10: vitamin A toxicity (cheilitis, xerosis, epistaxis, alopecia, increased skin fragility) ≥ 1/100 to < 1/10: conjunctivitis (be aware of contact lenses), hair loss, photosensitivity, hyperlipidemia.
Important drug interactions	Phenytoin, tetracycline, methotrexate, alcohol, minipill, lipid lowering drugs (see also table 30).
Special notes	Continue contraceptive use at least 2 years after cessation of medication in fertile women

Conclusions of the Dutch guidelines

EL: 2	Acitretin is effective in the treatment of adult patients with moderate to severe plaque psoriasis. 11% (A2) – 50% (B) of patients with psoriasis treated with 0.5 mg/kg/day acitretin reached PASI 90 response at week 8-12 and 25-41% of patients reached PASI 75 at week 8-12 when treated with 10-75 mg/day acitretin. *A2 Kragballe et al., 1989 (112)* *B Gupta et al., 1998 (113); van de Kerkhof et al., 1998 (114)*

Table 29 Important adverse effects of retinoids

Most frequently	Vitamin A toxicity (xerosis, cheilitis)
Frequently	Conjunctivitis (be aware of contact lenses), hair loss, photosensitivity, hyperlipidemia.
Sometimes	Muscular, joint and bone pain, retinoid-induced dermatitis
Rarely	Gastrointestinal complaints, hepatitis, jaundice. Bone changes with long-term use.
Very rarely	Idiopathic intracranial hypertension, decreased color vision, nyctalopia

Table 30 List of medication and drug interactions

Medicine	Type of drug interaction
Tetracycline	Induction of idiopathic intracranial hypertension
Phenytoin	Shift of plasma proteins
Vitamin A	Increasing the effect of retinoids
Methotrexate	Hepatotoxicity
Low dosage of pill with progesterone	Insufficient contraceptive effect
Lipid lowering drugs	Increased risk of myotoxicity
Antifungal imidazoles	Hepatotoxicity

Instructions for retinoid use

Prior to treatment
- Medical history and physical examination should be directed at muscle and skeletal problems. When patients experience symptoms supplementary imaging studies may be performed
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Exclude the possibility of pregnancy/lactation: patients have to be extensively informed about the teratogenic risk of the drug, the necessity of long-term effective contraceptives up to 2 years after cessation of acitretin therapy and the possible consequences of pregnancy during retinoid use: this must be well documented by the physician
- Patients should be informed about the specific risks of excessive alcohol consumption. Inform female patients about the increased conversion of acitretin into etretinate
- Direct the patient that blood donation is not allowed during and until 1 year after treatment
- Laboratory controls (Table 31)
-

Instructions for retinoid use

Prior to treatment
- Medical history and physical examination should be directed at muscle and skeletal problems. When patients experience symptoms supplementary imaging studies may be performed
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Exclude the possibility of pregnancy/lactation: patients have to be extensively informed about the teratogenic risk of the drug, the necessity of long-term effective contraceptives up to 2 years after cessation of acitretin therapy and the possible consequences of pregnancy during retinoid use: this must be well documented by the physician
- Patients should be informed about the specific risks of excessive alcohol consumption. Inform female patients about the increased conversion of acitretin into etretinate
- Direct the patient that blood donation is not allowed during and until 1 year after treatment
- Laboratory controls (Table 31)

During treatment
- Capsules should be taken during a meal or with milk
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- It is required to avoid pregnancy. Treatment is started at the second or third day of the menstruation cycle after adequate contraceptive use for at least 1 month prior to treatment. It is recommended to use 2 contraceptives simultaneously (e.g., condom + pill; IUD/NuvaRing + pill; note: avoid the use of preparations with low dose progesterone / mini-pill) during treatment and up to 2 years after cessation of treatment
- Avoid excessive usage of alcohol
- Ask patient about symptoms of the back and joints. When patients experience symptoms supplementary imaging studies may be performed
- Laboratory controls (Table 31)

After treatment
- Reliable contraceptives in fertile women up to 2 years after cessation of treatment
- It is recommended to use 2 contraceptives simultaneously, as stated above
- Patients are not allowed to be blood donors for 1 year after cessation of treatment

Table 31 Laboratory controls

Parameter	Prior to treatment	Treatment period (in weeks)					
		1	2	4	8	12	16
Blood count*	X				X		X
Liver values**	X		X	X	X		X
Serum creatinine	X						
Pregnancy test (urine)	X	Monthly during treatment					
Blood glucose (fasting)	X						
Tryglicerides, cholesterol, HDL	X			X			X

Further testing may be required based on clinical symptoms, risk and exposures

* Hb, Hct, leukocytes, thrombocytes
** ASAT, ALAT, AP, yGT

Treatment recommendation

0.5mg/kg/day acitretin is recommended for induction therapy of moderate to severe psoriasis.

When induction therapy is considered to be effective after 10 – 16 weeks, maintenance therapy may be considered using the lowest effective dosage.

When conventional systemic therapies are indicated, acitretin is not recommended as first-choice monotherapy.

Fertile women planning to have children should not be treated with acitretin owing to its teratogenic properties.

Fumaric acid esters

H.B. Thio, E.P. Prens

Table 32 Fumaric acid esters

Registration for psoriasis	1994 (Germany), not registered in the Netherlands
Recommended control parameters before starting treatment	Complete blood count, liver enzymes serum creatinine, urine sediment, pregnancy test.
Recommended initial dosage	See dosing scheme (Table 33)
Recommended maintenance dosage	Determine individually
Onset of effect	After 6 weeks
Response rate	18-46% PASI 90 after 16 weeks of treatment 50-70% PASI 75 after 16 weeks of treatment
Absolute contraindications (See SmPC)	Severe liver and/or kidney diseases, gastrointestinal diseases, hematological malignancies, pregnancy or breastfeeding
Relative contraindications (See SmPC)	Hematological diseases (deviation in blood count), simultaneous usage of drugs that have the potential to induce nephrotoxicity
Most common adverse effects (See SmPC)	≥ 1/10: diarrhea, flushing ≥ 1/100 to < 1/10: cramps, flatulence, lymphocytopenia, eosinophilia
Important drug interactions	No known drug interactions
Special notes	Especially applicable for long-term therapy

Conclusions of the Dutch guidelines

EL: 2	Fumaric acid esters result in almost complete remission in 24% (weighted average, 18-46%) of patients after 16 weeks of treatment. Partial remission (PASI 75) is seen in 50-70% of patients after 16 weeks of treatment. Good efficacy was reached in both short-term and long-term (maintenance) therapy. *A2 Altmeyer et al., 1994 (115); Gollnick et al., 2002 (116)* *B Nugteren-Huying et al., 1990 (117); Kolbach et al., 1992 (118); Nieboer et al., 1990 (119)* *C Altmeyer et al., 1996 (120); Bayard et al., 1987 (121); Litjens et al., 2003 (122); Carboni et al., 2004 (123); Mrowietz et al., 1999 (124)*

Table 33 Dosing scheme for dimethyl fumarate

Time	Dimethyl fumarate 30 mg Number of tablets / day	Dimethyl fumarate 120 mg Number of tablets / day
Week 1	0-0-1	-
Week 2	1-0-1	-
Week 3	1-1-1	-
Week 4	-	0-0-1
Week 5	-	1-0-1
Week 6	-	1-1-1
Week 7	-	1-1-2
	Evaluate clinical response: In case PASI response ≥ 50% In case PASI response ≤ 50%	 Maintain 1-1-2 Proceed to 2-1-2 (week 8)
Week 8	-	2-1-2
Week 9	-	2-2-2

Table 34 Important adverse effects of fumarates

Most frequently	Diarrhea, flushing
Frequently	Cramps, flatulence, lymphocytopenia, eosinophilia
Sometimes	Nausea, dizziness, headache, fatigue, proteinuria, increase of creatinine levels, increase of liver enzymes levels
Rarely	Isolated increase of ALAT or bilirubin

Instructions for use of fumaric acid esters

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination
- Laboratory controls (Table 35)

During treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination
- Laboratory controls (Table 35)

After treatment
- None

Table 35 Laboratory controls

Parameter	Prior to treatment	Treatment period (months)		3rd month, thereafter once every 3 months, followed by once every 6 months after 1 year of treatment
		1	2	
Total blood count (leucocytes, differential)	X	X	X	X
Liver enzymes (yGT, ALAT, ASAT)	X	X	X	X
Serum creatinine	X	X	X	X
Urea	X	X	X	X
Cholesterol	X	X	X	X
Urine sediment	X	X	X	X
Urine protein	X	X	X	X
Pregnancy test (urine)	X			

Treatment recommendation

Fumaric acid esters are recommended according to dosing scheme for induction therapy of patients with moderate to severe chronic plaque psoriasis.

When induction therapy is considered to be effective after 10 – 16 weeks, maintenance therapy may be considered using the lowest effective dosage.

Fumaric acid esters may be considered as first-choice systemic monotherapy.

2.5 Biologics

Biologics in general

T.E.C. Nijsten

Therapeutic response

The primary outcome in the evaluation for therapeutic response of psoriatic drugs remains the improvement of clinical disease severity (PASI 75 or PGA mild to absent), but patient-reported outcome measures (e.g. patient preference, treatment satisfaction and/or improvement in quality of life) are increasingly important [125]. The momentum of treatment evaluation is preferentially 24 weeks (initiation period),

but for some treatments this may be at 16 weeks (e.g. adalimumab and infliximab). When therapeutic response is considered suboptimal (PASI 75%-50% and PASI 50%) or insufficient by the patient several alternatives are possible: increase dosage or dosage frequency, combination therapy (for example adding topical therapies, UV-therapy and/or methotrexate or acitretin) or switch to another (biologic) therapy.

Transition

Clinical experience shows that switching between biologics of the same or different class may be effective in patients not responding to an anti-TNF alpha agent. Insufficient therapeutic response to a TNF-alpha antagonist does not imply ineffectiveness of the other biologics inhibiting TNF alpha. Of course patients can be switched to ustekinumab, a biologic with a completely different mode of action. The same applies vice versa. The evidence of the effectiveness of switching between biologics is derived from small observational studies and (retrospective) case series [126, 127].

Hepatitis / HIV

Owing to the immunosuppressive properties of biologics it is advised to exclude chronic and active infections with HBV, HCV, and HIV in patients with psoriasis before commencing biologic therapy. The following recommendations are based upon small case-series since solid clinical studies are lacking.

In chronic carriers of hepatitis B (HBsAg positive), there is a risk of reactivation of the virus (with the complication of acute liver failure). Therefore, these patients should not be treated with biologics, except when simultaneously treated with nucleoside analogues and guided by a gastrointestinal (GI) specialist.

In HCV infected patients with psoriasis, biologic therapy may be started with adequate monitoring and in consultation with a GI specialist. HCV, in contrast to HBV, lacks the possibility of integrating into the DNA of hepatocytes and thus the risk of HCV flares is absent.

In HIV infected patients with psoriasis, anti-TNF alpha therapy may be prescribed when the infection is controlled by HAART therapy. Additional controls are required given the possibility of drug interactions. Naturally, the patient should be treated in close consultation with the treating physician. Such experiences are lacking for ustekinumab therapy.

Malignancies

The risk of the occurrence of malignancies (especially lymphomas and cutaneous squamous cell carcinomas) related to immunosuppressive agents such as biologics remains an issue of concern. Patients with psoriasis may already have an increased risk of developing skin cancer because of prior UV-phototherapy (especially PUVA),

which is further increased after initiation of immunosuppressive drugs (e.g., cyclosporine and biologics) in patients with a history of high levels of UV exposure [128, 129, 130, 131]. Therefore, all patients and especially those with a prior history of intensive immunosuppressive therapy or PUVA therapy should be examined for melanoma and non-melanoma skin cancer prior to and during anti-TNF alpha treatment.
Spontaneous reporting registries have identified an increased risk of hepatosplenic T-cell carcinoma, which is often lethal, in patients using infliximab and adalimumab.
Long-term effects of ustekinumab are likely to be comparable to other biologics but relatively little is known because relatively few patients have used these drugs for a long period compared with the TNF antagonists. In clinical trials, some patients developed a basal cell carcinoma during ustekinumab treatment. Hence, screening for malignancies by physical examination (mainly the skin) and a complete blood sample is being advised before commencing therapy with ustekinumab.
In order to optimally assess the long-term safety and stimulating effects on the carcinogenesis of biologics well-designed and independent post-marketing studies (phase IV) are needed. Until now, few studies on the long-term safety are published [132, 133]. Large (inter)national prospective registers (e.g. PsoNet) of patients on biologic therapy may be helpful in detecting and estimating the risks associated with the use of biologics. Physicians are therefore encouraged to participate in patient registers (if available).

Demyelinating diseases
TNF-alpha antagonists are associated with the development or worsening of demyelinating diseases and multiple sclerosis.

Cardiovascular diseases
TNF-alpha antagonists are able to worsen (pre-existing) heart failure and should not be prescribed to patients with psoriasis with severe congestive heart failure (NYHA class III or IV). Patients with a mild form of heart failure being administered an anti-TNF alpha agent for psoriasis should be carefully monitored and also guided by a cardiologist.
Data from a meta-analysis seem to implicate a short-term increased risk for myocardial infarction, cerebrovascular accident, and cardiovascular mortality for ustekinumab (and briakinumab) [134]. Further studies are required, but this seems to be a specific complication of this class of biologics.

Infections
TNF-alpha antagonists increase the risk of infection including tuberculosis (TB). Reactivation of (latent) TB seems to occur more often with infliximab and adalimumab

therapy compared with etanercept. It is mandatory to screen for latent TB before commencing therapy with a biologic (see chapter: screening for tuberculosis). Other infections include upper and lower respiratory tract infections, urinary tract infections and skin infections [135].

Pregnancy
The experience with biologics just before and during pregnancy is too limited to claim safety of its (continuous) use.

Fertility
It is uncertain whether biologics reduce spermatogenesis [136, 137, 138]. No data has been published about the influence of TNF-alpha blockade on female fertility.

Transplacental passage
Biologics (adalimumab, infliximab and etanercept) may pass the placental barrier during the first, second, and especially third trimester [139].

Lactation
Mothers wishing to breastfeed their child have to be informed about the uncertainty of the influence of biologics on children and need to be advised about alternatives for lactation.

Biologics and antibody formation

L.L.A. Lecluse

As with other foreign proteins, treatment with biologics may cause antibody formation. Neutralizing antibodies have been shown against adalimumab, infliximab, and ustekinumab, but not against etanercept [132, 140, 141]. For adalimumab and infliximab routine screening can be done. Antibodies against ustekinumab are tested in an experimental setting at this moment.

When to check for antibodies
Assessment of antibody titer may be indicated in patients treated with adalimumab or infliximab when:
I There is a significant decrease in effectiveness of the agent involved
II The psoriasis is recalcitrant to improvement since commencing therapy
III An infusion reaction occurs (only with infliximab)

How to interpret and act on antibody titers

Situation I

The effectiveness of the biologic declines, the antibody titer is low, and serum concentration value of the biologic is decreased.

The biologic may be continued, but dosing frequency or dosage of this drug may be increased to reduce antibody formation. Costs of treatment will rise.

Situation II

There is no clinical sign of effectiveness of the biological agent, the antibody titer shows high levels of antibodies, and the biologic serum concentration is undetectable.

The biologic should not be continued because the antibodies are neutralizing the biological agent. Consider switching to a biologic of a similar or different therapeutic class.

Situation III

There is no clinical sign of effectiveness of the biological agent, the antibody titer shows no antibodies, and the biologic serum concentration is within normal range.

The patient does not respond to therapy. Consider switching to a biologic of a different therapeutic class.

Screening for tuberculosis

A.C.Q. de Vries, H. van Deutekom, T.E.C. Nijsten, Ph.I. Spuls

Table 36 Plan of action for tuberculosis screening

Diagnostic approach to TB, regardless of BCG vaccination status, prior to and during follow-ups of treatment with biologic agents. Physicians should be alert to the occurrence of TB during treatment and 6 months thereafter [142]. During treatment yearly screening is advised for latent TB. Medical history, Mantoux and IGRA are recommended. To limit the influence of immunosuppressive drugs on Mantoux and IGRA a treatment-free interval may be introduced a week before screening.

Medical history:
- Symptoms indicating possible TB
- Prior history of TB, possibly treated sufficiently
- Exposition to TB
- Originating from or recent long stay in an epidemic area
- Risk patient
- BCG vaccination status

Physical examination, consider:
- Auscultation of lungs when symptomatic (non-specific for TB diagnosis)
- Scar (left) upper arm (possible BCG vaccination)

Chest X-ray
- Signs of active or past TB?
  Consult pulmonologist in case of abnormalities

Mantoux
- ≥ 5mm induration → positive → consider latent TB infection (LTBI) or active TB infection (TBI) → consult pulmonologist
- < 5mm induration:
  - age < 65 years: draw blood for IGRA test
  - age ≥ 65 years: repeat Mantoux after 2 weeks
    - ≥ 5mm induration → positive → consult pulmonologist
    - < 5mm induration → draw blood for IGRA test

IGRA (Altena, 2010)

Mantoux	IGRA	Diagnosis	Management
< 5mm	Negative	Depending on medical history	- Start a biologic agent when medical history (symptoms, prior history, exposition, origin, recent stay, risk patient) reveals no signs of or risk to TB - In case medical history reveals signs of or risk to TB, consult a pulmonologist for further diagnostics and treatment - HIV-infected patients with a low CD-4 count could still have a TB infection
≥ 5mm < 10mm	Negative	Strongly consider LTBI and active TB	Consult pulmonologist for further diagnostics and treatment
> 10 mm	Negative	LTBI	Consult pulmonologist for further diagnostics and treatment
Every value	QFT-G 0.2-0.35 U/ml	Strongly consider LTBI	Consult pulmonologist for treatment
Every value	Positive (QFT-G > 0.35 U/ml)	LTBI	Consult pulmonologist for treatment

Treatment:
A
Active TB or (considered) LTBI → consult pulmonologist for treatment, in some cases for 9 months (143).
During treatment of LTBI a biologic agent may be started after 1-3 months. There is no consensus about this issue, thus, it is recommended to start treatment in consultation with a pulmonologist (142, 143).

B
Preference of biologic agent: (see also table 37) Studies suggest that reactivation of latent TB is less common in etanercept compared with adalimumab or infliximab (143, 144). This could be related to the different mode of action and binding to TNF-alpha. For ustekinumab, at present, there is no available data.

Table 37 Biologic agents classified by TB risk

High risk (143, 144)	Infliximab Adalimumab Prednisone ≥ 15mg/day Cytostatic agents
Average risk (143, 144)	Etanercept
Low risk	Methotrexate (one case reported at Lareb) Cyclosporine (one case reported at Lareb)
Too little evidence	Ustekinumab

Adalimumab

H.B. Thio

Table 38 Adalimumab

Registration for psoriasis	December 2007 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, erythrocyte sedimentation (ESR) / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV (prior to treatment). TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	Loading dosage: 80 mg subcutaneous
Recommended maintenance dosage	40 mg subcutaneous 1x every 2 weeks
Onset of effect	After 4 weeks
Response rate	53-80% PASI 75 24-52% PASI 90
Absolute contraindications (See SmPC)	Hypersensitivity to adalimumab, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III, CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.

Table 38 Continued

Most common adverse effects (See SmPC)	≥ 1/10: respiratory tract infections (including lower and upper respiratory tract infections, pneumonia, sinusitis, pharyngitis, nasopharyngitis, and viral herpes pneumonia), leucopenia (including neutropenia, agranulocytosis), anemia, increased lipid levels, headache, abdominal pains, nausea and vomiting, increased liver enzymes, rash (including scaly rash), myalgia, injection site reactions (including injection site erythema). ≥ 1/100 to < 1/10: systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including viral gastroenteritis), skin and subcutaneous infections (including paronychia, cellulitis, impetigo, necrotizing fasciitis and herpes zoster), etc. (see SMPC or http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
Important drug interactions	Abatacept, Anakinra
Special notes	Vaccination with live vaccines should not be administered during treatment with a biologic. Depending on the drug's half-life, the biologic must be stopped 4-8 weeks prior to immunization and may be restarted 2-3 weeks after vaccination.

Conclusions of the Dutch guidelines

EL: 1	Adalimumab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. After 16 weeks of treatment (Gorden et al., at week 12), PASI 75 was reached in 53-80% and PASI 90 in 24-52% of patients with psoriasis treated with adalimumab. *A2 Gordon et al., 2006 (145); Menter et al., 2008 (146); Saurat et al., 2008 (103)*

Table 39 Important adverse effects of adalimumab

Most frequently	Injection site reactions, respiratory tract infections, headache, abdominal pains, nausea and vomiting, rash, myalgia, bone marrow depression
Frequently	(Severe) infections, benign tumors, skin cancer, mood swings (inter alia depression), anxiety, fatigue, sensory disturbances, migraine, dizziness, itch, pyrosis
Sometimes	Tuberculosis, lymphoma
Rarely	-
Very rarely	Drug-induced lupus, sudden cardiac death, multiple sclerosis

Table 40 List of medication and drug interactions

Medicine	Type of drug interaction
Anakinra	Increased risk on serious infection
Immunosuppressive mediation (cyclosporine, other biologics)	Increased immunosuppression
PUVA	Risk of skin cancer

Instructions for adalimumab use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 41)
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
- Contraception

During treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 41)
- Urine sediment
- Contraception

After treatment
- After treatment with adalimumab physicians are advised to perform regular follow-ups with medical history and physical examination
- Reliable contraceptives until 5 months after treatment, if indicated
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics

Table 41 Laboratory controls

Parameter	Prior to treatment	Treatment period (weeks)		Thereafter once every 3 months
		4	12	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X	X
Pregnancy test (urine)	X	X	X	X
HBV / HCV	X			
HIV	X			

Further testing may be required based on clinical symptoms, risk and exposures

Treatment recommendation

Adalimumab is recommended for induction therapy (80 mg at week 0, followed by 40 mg every 2 weeks) in patients with moderate to severe chronic plaque psoriasis, when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated.

Etanercept

T.E.C. Nijsten

Table 42 Fumaric acid esters

Registration for psoriasis	September 2004 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	2x25 mg/week, 1x50 mg/week or 2x50 mg/week (week 0-12)
Recommended maintenance dosage	2x25 mg/week, 1x50 mg/week or 2x50 mg/week
Onset of effect	After 6-8 weeks
Response rate	PASI 75 in 33 or 49% after 12 weeks (2x25 or 2x50 mg/week)
Absolute contraindications (See SmPC)	Hypersensitivity to etanercept, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III, CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: infections (including lower and upper respiratory tract infections, pneumonia, bronchitis, cystitis and skin infections), injection site reactions (including bleeding, bruising, erythema, itch, pain, swelling). ≥ 1/100 to < 1/10: allergic reactions, auto-antibody formation, pruritus, fever.
Important drug interactions	Anakinra, Abatacept, immunosuppressives (cyclosporine, other biologics), PUVA.
Special notes	Weight gain

Conclusions of the Dutch guidelines

EL: 1	Etanercept is effective for the treatment of moderate to severe plaque psoriasis in adult patients. At week 12, PASI 75 was reached in 30-34% and PASI 90 in 11% of patients when etanercept was prescribed in a dosage of 2 x 25 mg per week. When 2 x 50 mg etanercept is administered, PASI 75 and PASI 90 are reached in 47-49% and 21% of patients, respectively, at week 12. These percentages increase with 10% at week 24. *A2 Gottlieb et al., 2003 (147); Leonardi et al., 2003 (148); Tyring et al., 2006 (149); Papp et al., 2005 (150)*

Table 43 Important adverse effects of etanercept

Most frequently	Infusion reactions, infections (upper respiratory tract, bronchitis, skin infections)
Frequently	Pruritus, antibody formation, allergy
Sometimes	Thrombocytopenia, urticaria, angioedema, severe infections (for example: pneumonia, cellulitis and sepsis), uveitis, Non-melanoma skin cancer, interstitial lung disease, rash
Rarely	Anemia, leucopenia, neutropenia, pancytopenia, vasculitis, subacute and discoid LE, demyelinating disease, TB reactivation, convulsions, heart failure, severe allergy, liver function abnormalities
Very rarely	Aplastic anemia

Table 44 List of medication and drug interactions

Medicine	Type of drug interaction
Anakinra	Neutropenia and severe infections
Immunosuppressive mediation (cyclosporine, other biologics)	Increased immunosuppression
PUVA	Risk of skin cancer (especially squamous cell carcinoma)

Instructions for etanercept use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 45)
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
- Contraception

Instructions for etanercept use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)

- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 45)
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
- Contraception

During treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 45)
- Urine sediment
- Contraception

After treatment
- After treatment with etanercept physicians are advised to perform regular follow-ups with medical history and physical examination
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics

Table 45 Laboratory controls

Parameter	Prior to treatment	Treatment period (weeks)		Thereafter once every 3 months
		4	6	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X	X
Pregnancy test	X	X	X	X
HBV / HCV	X			
HIV	X			

Further testing may be required based on clinical symptoms, risk and exposures

Treatment recommendation

Etanercept is recommended for induction therapy (2 x 25 mg, 1 x 50 mg or 2 x 50 mg per week) (maximum of 24 weeks) in patients with moderate to severe chronic plaque psoriasis, when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated.

When induction therapy with etanercept is effective after 10-16 weeks, low dose etanercept (2 x 25 mg per week or 1 x 50 mg per week) should be prescribed as maintenance therapy.

Infliximab

M. de Groot

Table 46 Infliximab

Registration for psoriasis	September 2005 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	5 mg/kg body weight
Recommended maintenance dosage	5 mg/kg body weight week 2, 6, and thereafter every 8 weeks
Onset of effect	After 2-5 weeks
Response rate	PASI 75 in 80% of patients after 10 weeks
Absolute contraindications (See SmPC)	Hypersensitivity to infliximab, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III and CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: none ≥ 1/100 to < 1/10: viral infections (e.g., flu, viral herpes infection), serum sickness-like symptoms, headache, vertigo, dizziness, flush, lower respiratory tract infection (e.g., bronchitis, pneumonia), upper respiratory tract infections, sinusitis, dyspnoea, abdominal pains, diarrhea, nausea, dyspepsia, elevated transaminases, urticaria, rash, pruritus, hyperhidrosis, dry skin, infusion related reactions, chest pain, fatigue, fever

Table 46 Continued

Important drug interactions	Abatacept, Anakinra
Special notes	Reliable contraceptives in fertile women until 6 months after infliximab treatment

Conclusions of the Dutch guidelines

EL: 1	Infliximab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. About 64% - 88% of patients treated with 5mg/kg infliximab reached PASI 75 at week 10. About 41% - 57% of patients treated with infliximab (5mg/kg) reached PASI 90 at week 10. *A2 Antoni et al., 2005 (151); Menter et al., 2007 (152); Reich et al., 2005 (153); Gottlieb et al., 2004 (154)*

Table 47 Important adverse effects of infliximab

Most frequently	Infusion reactions, infections, nausea, diarrhea, difficulty breathing, dizziness, fatigue
Frequently	Headache, flushing, pruritus, urticaria, fever, elevated transaminases
Sometimes	Serum sickness-like disease, cutaneous lupus erythematosus, severe infections, anaphylactic reaction, circulation problems, depression
Rarely	Opportunistic infections, tuberculosis, pancytopenia, vasculitis, demyelinating diseases
Very rarely	Myelitis transversa, psoriasis (including pustular psoriasis), hepatocellular damage. In patients with Crohn's disease and ulcerative colitis hepatosplenic T-cell lymphoma may be induced.

Instructions for infliximab use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:

- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 48)
- Urine sediment
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
· Contraception

During treatment
· Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
· Perform a TB screening annually (medical history, mantoux and IGRA)
· Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
· Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms
· Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 48)
- Urine sediment
· Contraception

After treatment
· After treatment with infliximab physicians are advised to perform regular follow-ups with medical history and physical examination
· Reliable contraceptives until 6 months after cessation of treatment, if indicated
· Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics

Table 48 Laboratory controls

Parameter	Prior to treatment	Treatment period (weeks)		Thereafter, prior to every infusion
		4	6	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X	X
Pregnancy test	X	X	X	X
HBV / HCV	X			
HIV	X			

Further testing may be required based on clinical symptoms, risk and exposures

Treatment recommendation

Infliximab is recommended for induction therapy when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated. It is advised to prescribe infliximab 5mg/kg in patients with moderate to severe chronic plaque psoriasis at week 0, 2, 6, and every 8 weeks thereafter.

When induction therapy with infliximab is effective after 10-16 weeks, maintenance therapy with infliximab is recommended for every 8 weeks.

It is advised to combine infliximab therapy with 7.5 mg methotrexate per week in order to prevent antibody formation and to lower the risk of infusion reactions.

Ustekinumab

Ph.I. Spuls, P.A. Poblete-Gutiérrez, J. de Bes

Table 49 Ustekinumab

Registration for psoriasis	20th November 2008 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	45 mg, patients > 100 kg 90 mg at week 0, 4 and 16
Recommended maintenance dosage	45 mg/12 weeks, patients > 100 kg 90 mg/12 weeks
Onset of effect	After 2 weeks
Response rate	PASI 75 in 66-76% of patients
Absolute contraindications (See SmPC)	Hypersensitivity to ustekinumab, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III and CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II) and a prior history of or increased risk for cardiovascular accident or acute myocardial infarction. Hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: nasopharyngitis and upper respiratory tract infections ≥ 1/100 to < 1/10: inflammation of subcutaneous connective tissue (cellulitis), viral infection of the upper respiratory tract, hypersensitivity reactions (including rash and urticaria), depression, dizziness, headache, sore throat, stuffy nose, diarrhea, pruritus, back pain, myalgia, fatigue, erythema on injection site

Table 49 Continued

Important drug interactions	Unknown
Special notes	Reliable contraceptives are mandatory in fertile women until 15 weeks after ustekinumab treatment

Conclusions of the Dutch guidelines

EL: 1	Ustekinumab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. PASI 75 was reached in 67% of patients treated with ustekinumab (45 mg at week 0, 4 and 16) at week 12. PASI 75 was reached in 66-76% of patients treated with ustekinumab 90 mg (week 0, 4 and 16). A maximum effect was observed in more than three-quarters of the research population (PASI 75) after 24 weeks. *A2 Leonardi et al., 2008 (155); Papp et al., 2008 (132)*

Table 50 Important adverse effects of ustekinumab

Most frequently	Nasopharyngitis, upper respiratory tract infections, headache, arthralgia
Frequently	Cellulitis, viral infections of upper respiratory tract, depression, dizziness, headache, sore throat, stuffy nose, diarrhea, pruritus, back pain, myalgia, fatigue, erythema on injection site, urticaria
Very rarely	Severe infections or allergy

Instructions for ustekinumab use

Prior to treatment
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, TB, heart and kidney diseases and neurological symptoms
- Recommended actions are:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory controls (Table 51)
  - Urine sediment
  - Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
  - Vaccinations in concordance with the National Immunization Program

- Pregnancy test
- Reliable contraceptives in fertile women during treatment and until 15 weeks after cessation of treatment

During treatment (every 3 months)
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Recommended actions are:
- Check for skin cancer
- Laboratory controls (Table 51)
- Urine sediment

After treatment
- Follow-up visits for assessing symptoms of psoriasis
- Reliable contraceptives until 15 weeks after cessation of treatment, if indicated
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics

Table 51 Laboratory controls

Parameter	Prior to treatment	After 4 weeks	Thereafter once every 12 weeks
Total blood count	X	X	X
Liver enzymes	X	X	X
Serum creatinine	X	X	X
Urine sediment	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X
Pregnancy test	X	X	X
HBV / HCV	X		
HIV	X		

Further testing may be required based on clinical symptoms, risk and exposures

Considerations when prescribing biologics

T.E.C. Nijsten

The following table highlights the considerations per biologic.

Table 52 Considerations when prescribing biologics

Etanercept (E)	Adalimumab (A)	Infliximab (I)	Ustekinumab (U)
Less efficacy compared with A, I and U. However, maximum efficacy may be reached after 24 weeks	Higher efficacy compared with E (after 12 and 24 weeks)	Higher efficacy compared with E (after 12 and 24 weeks)	Higher efficacy compared with E (after 12 and 24 weeks)
		Fast initial response	
Less effective than U	No head-to-head trials with this biologic	No head-to-head trials with this biologic	More effective than E
Drug survival rate below I (daily practice data)	Drug survival rate below I (daily practice data)	Highest drug survival rate compared with A and E (daily practice data)	Drug survival rate is high during 1 year (daily practice data)
Injection site reaction	Injection site reaction	Infusion reaction	Injection site reaction
Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia
Less TB reactivation compared with A and I	More TB reactivation compared with E	More TB reactivation compared with E	Little long-term experience
Non-neutralizing antibody formation	Neutralizing antibody formation, possibly clinically relevant	Neutralizing antibody formation, clinically relevant	
High dosage (2x50 mg/week) leads to high costs	Loading dosage at start increases cost at start.	In extreme obese patients (> 100kg) costs will rise. Loading dosage at start increases cost at start.	In extreme obese patients (> 100kg) costs will rise. Loading dosage at start increases cost at start.

Table 52 Continued

Etanercept (E)	Adalimumab (A)	Infliximab (I)	Ustekinumab (U)
			Long treatment interval (3 months). (Higher user friendliness)
Daily practice data indicate biologics to be less effective when compared with data from randomized controlled trials. Hence, the dosage of biologics is higher in daily practice.			

This table is a summary of the paragraph "considerations when prescribing biologics" within the Dutch guidelines on the treatment of psoriasis 2011 (http://www.huidarts.info/documents/uploaded_file.aspx?id=579). The content of this table is based upon the following references: [125-127, 134, 156-160].

Conclusions

Adalimumab or low-dose etanercept (1x50 mg/week) are the preferred first-choice treatments in otherwise healthy, biologic-naïve patients with psoriasis. Adalimumab seems to be more effective than etanercept in the short-term, but may be related to clinically relevant antibody formation. Infliximab is preferred in acute situations (e.g., severe exacerbation of plaque psoriasis, off-label for psoriatic erythroderma or generalized pustular psoriasis) because of high efficacy and fast clinical response, followed by a maintenance dosage of this agent. Also, infliximab is important in patients not responding to other TNF-alpha agents. Although ustekinumab is highly effective, the working group holds the opinion that until long-term efficacy and safety are elucidated this agent should be reserved for patients responding insufficiently to TNF-alpha antagonists.

3. Treatment of psoriasis of the face and flexures

P.C.M. van de Kerkhof, C.L.M. van Hees

Epidemiology

Conclusions of the Dutch guidelines

EL: 3	Psoriasis of the face is present in 17-46% and psoriasis of the flexures in 6.8-36% of patients with psoriasis. Hence, psoriasis cannot be regarded as a rare manifestation in these areas. *C Fauéré et al., 2005 (161); Dubertret et al., 2006 (162); van de Kerkhof et al., 2000 (163); Farber et al., 1968 (164); Farber et al., 1974 (165); Wang et al., 2005 (166); Nanda et al., 1990 (167); Puissant, 1970 (168); Nyfors et al., 1975 (169)* *D van de Kerkhof et al., 2007 (10)*

Recommendation

It is recommended to further study the efficacy and safety of treatments (preferably by randomized, double blind, controlled trials), given the frequency of psoriasis of the face and flexures.

Clinical signs

Conclusions of the Dutch guidelines

EL: 4	Psoriasis of the face is a prognostic marker for a severe form of psoriasis. Psoriasis of the flexures is not a prognostic marker. *C Park et al., 2004 (170)* *D van de Kerkhof et al., 2007 (10)*

EL: 4	Psoriasis of the face and psoriasis of the flexures should not be considered two different disease entities, but as a variation of localization of the same disease. *D van de Kerkhof et al., 2007 (10)*

EL: 3	Clinical signs of facial psoriasis suggest there are three forms: hairline psoriasis, sebo-psoriasis and true facial psoriasis. *C Woo et al., 2008 (171)* *D van de Kerkhof et al., 2007 (10)*

EL: 4	Otitis externa and ocular manifestations may drastically decrease quality of life and should therefore not be neglected. *D van de Kerkhof et al., 2007 (10)*

Pathogenetic aspects

Conclusions of the Dutch guidelines

EL: 3	Evidence is small to absent on the role of microbiological factors in the pathogenesis of psoriasis of the face and flexures. *C Rosenberg et al., 1989 (172)* *D van de Kerkhof et al., 2007 (10)*

EL: 3	The reaction to UV radiation differs between patients with facial psoriasis. At least 5% of patients with psoriasis has photosensitive psoriasis. *C Farber et al., 1968 (164); Farber et al., 1974 (165); Lane et al., 1937 (173); Lomholt et al., 1963 (174); Braun-Falco et al., 1972 (175)* *D van de Kerkhof et al., 2007 (10)*

Recommendation

It is recommended to exclude photosensitive diseases such as lupus erythematosus and polymorphic light eruption in patients with photosensitive psoriasis.

Antimicrobial treatment

Conclusions of the Dutch guidelines

EL: 3	There is no evidence that antimicrobial treatment is effective for psoriasis of the flexures. *C Leigheb et al., 2000 (176)*

EL: 3	There is evidence antifungal treatment may be effective for sebo-psoriasis of the face. *C Doering., 1985 (177); Faergemann, 1985 (178)*

Considerations

The efficacy of antiseptic, antibacterial, and antifungal treatments has sparsely been investigated in comparing studies. Randomized and double blind trials are lacking.

Treatment recommendation

Antimicrobial treatment is not indicated for the treatment of psoriasis of the face and flexures.

Dithranol and coal tar

Conclusions of the Dutch guidelines

EL: 3	The efficacy of dithranol combined with coal tar is similar as for fluocinolone acetonide cream. *B Heller, 1989 (179)*

Considerations

The evidence of the efficacy of dithranol is also being supported by decades of clinical experience.

Skin irritation and stains in textile limit the use of these treatments.

Treatment recommendation

Discoloration and skin irritation limit the use of dithranol and coal tar. Dithranol and coal tar are not indicated for first-line therapy, except in cases in which first-line therapies fail.

Topical corticosteroids

Conclusions of the Dutch guidelines

EL: 3	Evidence about the efficacy and safety of topical corticosteroids comes from a non-comparative study (topical corticosteroids until 12 weeks) and a double blind, randomized vehicle-controlled study (topical corticosteroids during 4 weeks). *B Kreuter et al., 2006 (180)* *C Lebwohl et al., 2001 (181)*

Considerations

Textbooks state that low-potent (class 1-2) topical corticosteroids are effective and safe, whereas mid-potent (class 2-3) topical corticosteroids induce perioral dermatitis and striae, especially during long-term use.

Treatment recommendation

Topical corticosteroids class 1-2 (low-potency) are first-choice treatments for psoriasis of the face and flexures during a limited treatment period. Subsequently, topical non-steroidal agents should be prescribed.

Vitamin D3 analogues

Conclusions of the Dutch guidelines

EL: 2	Vitamin D analogues are effective for the treatment of psoriasis of the face and flexures. *A2 Liao et al., 2007 (182)* *B Ortonne et al., 2003 (183)* *C Duweb et al., 2003 (184); Kienbaum et al., 1996 (185); Langer et al., 1996 (186)*

EL: 3	Calcitriol is superior over calcipotriol regarding safety profile. *B Ortonne et al., 2003 (183)*

Treatment recommendations

Vitamin D3 analogues are first-choice treatments for psoriasis of the face and flexures. Calcitriol induces less adverse effects, such as erythema and irritation, than calcipotriol.

Calcineurin inhibitors

Conclusions of the Dutch guidelines

EL: 1	The efficacy of calcineurin inhibitors for the treatment of psoriasis of the face and flexures has been assessed in 4 independent A2-studies (2 placebo-controlled studies, 1 comparative study with clobetasone butyrate and 1 comparative study with calcitriol). *A2 Lebwohl et al., 2004 (187); Gribetz et al., 2004 (188); Kleyn et al., 2005 (189); Liao et al., 2007 (182)*

Considerations

Calcineurin inhibitors are not registered for this treatment indication.

Treatment recommendations

Low-potent (class 1-2) topical corticosteroids *during 2-4 weeks* are the first-choice treatment of psoriasis of the face and flexures. Calcineurin inhibitors or Vitamin D3 analogues may also be prescribed. Calcineurin inhibitors may be used for long-term treatment.

Photo(chemo)therapy

Conclusions of the Dutch guidelines

EL: 4	No studies have been conducted measuring the efficacy and safety of photo(chemo)therapy. However, clinical experience shows these treatments improve psoriasis of the face and flexures. *D van de Kerkhof et al., 2007 (10)*

Treatment recommendations

When topical therapies provide insufficient disease control, phototherapy is an option for the treatment of psoriasis of the face and flexures.

Systemic therapies

Conclusions of the Dutch guidelines

EL: 4	No studies have been conducted measuring the efficacy and safety of methotrexate, cyclosporine, acitretin, fumaric acid esters and biologics for the treatment of psoriasis of the face and flexures. However, clinical experience shows these treatments improve psoriasis in these locations. *D van de Kerkhof et al., 2007 (10)*

EL: 3	There is evidence available indicating botulinum toxin is effective for the treatment of psoriasis of the flexures. *C Zanchi et al., 2008 (190)*

Considerations

Botulinum toxin is not registered for the treatment of psoriasis. The costs of this treatment are substantial.

Treatment recommendations

When topical therapies provide insufficient disease control, systemic therapies are an option.

4. Treatment of childhood psoriasis

M.M.B. Seyger

Introduction

All drugs mentioned in these guidelines have not been registered for the treatment of childhood psoriasis. Thus, usage of these drugs is off-label, with the exception of etanercept, which is registered for plaque psoriasis in children aged eight years or older. Off-label use of drugs is not uncommon, according to the Medicine Evaluation Board (MEB; Netherlands: CBG) and Inspection for Health Care (IGZ), if justified. The treating physician is obligated to inform the patient about the advantages and disadvantages of off-label drug use.

Topical corticosteroids

Conclusions of the Dutch guidelines

EL: 3	Halobetasol cream 0.05% and clobetasol proprionate emulsion 0.05% twice daily may be effective treatments for childhood psoriasis. Reported adverse effects during treatment were relatively mild. *C Herz et al., 1991 (191); Kimbal et al., 2008 (192)* *D Feicht, 1982 (193)*

Considerations

Published literature on the use of topical corticosteroids in childhood psoriasis is scarce. The number of treated patients is low and the treatment period short. Also, different vehicles were being used. Nonetheless, topical corticosteroids are important in the physician's treatment arsenal for treating childhood psoriasis.

Treatment recommendations

The use of topical corticosteroids is rewarding in childhood psoriasis. It is recommended to use topical corticosteroids of class 2-3 (mild-potency).

Vitamin D3 analogues

Conclusions of the Dutch guidelines

EL: 3	Calcipotriol is an effective and mostly well tolerated treatment option for plaque type childhood psoriasis. Adverse effects are mild. *A2 Oranje et al., 1997 (194)*

EL: 3	Calcitriol seems to be an effective treatment for childhood psoriasis with mild adverse effects. *B Perez et al., 1995 (195)*

Considerations

Both calcipotriol and calcitriol are not registered for use in children. Calcipotriol is no longer available as monotherapy in the Netherlands.

Treatment recommendations

Given the efficacy and mild adverse effect profile of Vitamin D3 and analogues (calcipotriol), these agents are recommended as first-choice therapy for childhood psoriasis. A combination with topical corticosteroids class 2-3 (mild potency) is recommended.

Calcineurin inhibitors

Conclusions of the Dutch guidelines

EL: 3	Tacrolimus 0.1% seems to be effective and safe for short-term treatment of childhood psoriasis of the face and flexures. Long-term efficacy has not been described in studies. *C Brune et al., 2007 (196); Steele et al., 2005 (197)*

EL: 3	Due to small numbers of treated patients, no conclusions can be drawn on the use of pimecrolimus for childhood psoriasis. *C Amichai, 2004 (198); Mansouri et al., 2006 (199)*

Considerations

Studies covered by these guidelines only describe the efficacy of 0.1% tacrolimus in children with psoriasis of the face and flexures. Calcineurin inhibitors are not registered for this treatment indication. In children (≤ 16 years) with eczema, tacrolimus 0.03% is registered.

Treatment recommendations

It is recommended to consider treatment with tacrolimus 0.03% or 0.1% in children with therapy resistant psoriasis of the face and flexures.

Dithranol

Conclusions of the Dutch guidelines

EL: 3	Dithranol is effective and safe for treatment of childhood psoriasis. *C Zvulunov et al., 1994 (200); Guerrier et al., 1983 (201)* *D Schubert et al., 2007 (202)*

Considerations

To reduce the risk of adverse effects (discolorations and skin irritation) dithranol should be used in a daycare unit setting. This also increases compliance and guarantees a more effective treatment regimen.

Treatment recommendations

It is strongly recommended to prescribe dithranol treatment for children with psoriasis if treatment with topical corticosteroids and vitamin D3 analogues failed. This should preferably take place in a daycare unit.

Phototherapy

Conclusions of the Dutch guidelines

EL: 3	Narrowband UVB treatment for children with plaque psoriasis or guttate psoriasis has positive results and a relatively mild adverse effect profile during a mean treatment period of 12 weeks. *C Al-Fouzan et al., 1995 (203); Jain et al., 2007 (204); Jury et al., 2006 (205); Pasic et al., 2003 (206); Tay et al., 1996 (207)*
No conclusion possible	Evidence on the efficacy of PUVA treatment for childhood psoriasis is too limited. *D Kim et al., 1998 (208); Thappa et al., 2006 (209)*

Considerations

Uncertainty persists on the long-term safety of UVB phototherapy. UVB therapy results in actinic damage and premature skin aging. UVB is carcinogenic. Oral PUVA has a carcinogenic effect.

Treatment recommendations

It is recommended to limit the use of UVB phototherapy in children with psoriasis. Especially in children less than 12 years of age and a fair skin type, UVB should be considered with great care. PUVA therapy is contraindicated in children with psoriasis given its carcinogenic effect.

Antibiotics

Conclusions of the Dutch guidelines

EL: 3	The efficacy of oral antibiotics and its use in children with guttate psoriasis remains controversial. *C Patrizi et al., 1994 (210)* *D Pacifico, 1993 (211)*

Considerations

If, on anamnesis, the psoriatic plaques erupted after a severe throat infection or the psoriasis deteriorated after a throat infection, it is recommended to perform a throat culture.

Treatment recommendations

When, on anamnesis, a throat infection may have induced or worsened the psoriasis and the performed throat culture is positive, it is recommended to consider the use of oral antibiotics.

Retinoids

Conclusions of the Dutch guidelines

EL: 3	Etretinate is effective in treating pustular or erytrodermic psoriasis. However, adverse effects are frequently encountered. *C Rosinska et al., 1988 (212); van de Kerkhof, 1985 (213); Pavicic et al., 1986 (214); Kim et al., 1991 (215); van der Rhee et al., 1980 (216)*
No conclusion possible	The use of acitretin in childhood psoriasis has not been thoroughly studied. Therefore, no conclusions can be stated in these guidelines. However, given the positive experiences with etretinate, it is likely that acitretin is also effective in pustular and erythrodermic childhood psoriasis.

Considerations

Etretinate is no longer available. Acitretin is a metabolite of etretinate, therefore, the efficacy of acitretin is probably similar to etretinate. Considerations about general safety are described in the chapter of retinoids in the full Dutch S3-guidelines: http://www.huidarts.info/documents/uploaded_file.aspx?id=579. Special attention should be given to the occurrence of skeletal toxicities in children on long-term retinoid therapy [217].

Treatment recommendations

It is recommended to consider the use of acitretin in children with pustular or erytrodermic psoriasis. It is firmly recommended not to treat adolescent women, given the potential teratogenic effects.

Treatment with acitretin may be considered in other types of childhood psoriasis.

Cyclosporine

Conclusions of the Dutch guidelines

EL: 3	The described efficacy of cyclosporine treatment in childhood psoriasis is ambiguous. Safety aspects were sparsely described. *C Mahe et al., 2001 (218); Kilic et al., 2001 (219); Alli et al., 1998 (220); Torchia et al., 2006 (221)*

Considerations

Adverse effects of cyclosporine in children with psoriasis were sparsely described in studies. In children with atopic dermatitis, this agent was well tolerated for a period of one year [222]. Given the potential cumulative toxicity, especially children should be treated with caution [223].

Treatment recommendations

Given the previous considerations and the contradictive evidence on cyclosporine for childhood psoriasis, it is recommended to use this agent only in exceptional cases.

Methotrexate

Conclusions of the Dutch guidelines

EL: 3	Methotrexate is effective for the treatment of moderate to severe childhood psoriasis. Most evidence is on plaque psoriasis. Short-term adverse effects are relatively mild and can easily be treated. *C Collin et al., 2006 (224); Kaur et al., 2008 (225); Kumar et al., 1994 (226); Kalla et al., 1996 (227); Dogra et al., 2004 (228); Dogra et al., 2005 (229); Ivker et al., 1993 (230)*

Considerations

Long-term safety of methotrexate for childhood psoriasis has not been studied. However, this drug has been used for decades for the treatment of juvenile idiopathic arthritis without severe adverse effects. Therefore, this treatment is considered safe [231].

Treatment recommendations

Methotrexate is recommended as first-choice systemic treatment in children with moderate to severe plaque psoriasis. Dosage is between 0.2-0.4 mg/kg/week. Folic acid 5mg should be administered 24 hours after methotrexate intake. Methotrexate should not be administered with milk products as this negatively affects its efficacy.

Biologics

Conclusions of the Dutch guidelines

EL: 3	Etanercept is effective for the treatment of plaque psoriasis in children. Dosage was 0.8 mg/kg/week. Short-term adverse effects are usually infections. *A2 Paller et al., 2008 (232)*
No conclusion possible	Infliximab seems effective for induction of remission. However, firm conclusions cannot be made on the results of 4 patients. *D Pereira et al., 2006 (233); Farnsworth et al., 2005 (234); Menter et al., 2004 (235); Weishaupt et al., 2007 (236)*

Considerations

Knowledge on long-term adverse effects of biologics is insufficient. It is unknown whether biologics increase the risk of lymphoma and skin cancer in patients with psoriasis. The safety and effectiveness of etanercept was registered for children with juvenile idiopathic arthritis during 8 consecutive years. In these 8 years, the authors found no increase of severe adverse effects [231].

Treatment recommendations

Given the uncertainty concerning long-term safety of biologics, care should be taken in prescribing these agents in children with moderate to severe psoriasis. Etanercept is recommended when topical therapies, e.g. dithranol, as well as UVB (in older children) and methotrexate are ineffective, contraindicated, or not being tolerated.
The working group holds the opinion that children treated with etanercept should be registered in a national database to evaluate long-term safety.

Other topical and systemic therapies

Conclusions of the Dutch guidelines

No conclusion possible	No conclusions can be drawn on the efficacy and safety of Chinese drugs, excimer laser, tazarotene, wratizolin, fumaric acid esters, dapsone, prednisone, tonsillectomy and colchicine. *C Lin et al., 2006 (237); Pahlajani et al., 2005 (238); Diluvio et al., 2007 (239); Michalowski et al., 1983 (240); Gunther et al., 2004 (241); Yu et al., 2001 (242); Fernandes-El et al., 2000 (243); Tsuge et al., 1995 (244); McMillin et al., 1999 (245); Hone et al., 1996 (246); Wahba et al., 1980 (247); Zachariae et al., 1982 (248)*

Considerations

None

Treatment recommendations

No conclusions can be drawn from the literature on the efficacy and safety of other therapies. These therapies are not recommended.

5. The patient's perspective

J. de Korte, O.D. van Cranenburgh

The experiences and opinions of patients with chronic skin diseases are becoming increasingly important for the assessment of their general and skin-related health status, and for the treatment of their skin disease. These patients' perspectives are generally captured with so-called Patient Reported Outcomes (PROs). PROs are reports or assessments of any aspect of a patient's health status and/or treatment impact that are directly expressed by the patient, i.e. without the interpretation of others [249]. Examples of PROs are: disease severity, health-related quality of life, cost-benefit, safety, compliance, treatment preference, and satisfaction with treatment. Health-related quality of life (HRQoL) of patients with psoriasis, i.e. the physical, emotional and social functioning and well being of patients, has been referred to throughout the Dutch S3-guidelines on the treatment of psoriasis 2011. The practice guidelines 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis' 2003 (updated 2005 and 2009) also addressed that, in exceptional cases, patients with less severe psoriasis may be prescribed a biological agent when there is a considerable loss of quality of life (Skindex-29 ≥ 35, combined with a PASI ≥ 8) (6).
In order to gain insight into psoriasis patients' satisfaction with treatment, we conducted a cross-sectional, national, web-based, survey. Aims of this survey were to assess the degree of patients' satisfaction with prior and current dermatological treatments and to study how patients value 1) effectiveness, 2) safety, 3) convenience

and 4) organization of treatment, 5) information about treatment, and 6) the doctor-patient relationship.

Our study comprised 2070 patients (response rate: 43%), aged ≥ 18 years, with a self-reported diagnosis of psoriasis and treated or being treated with topicals, phototherapy, and/or systemic therapies. The questionnaire survey was preceded by literature search, results from a focus group session (N=9), and results from a previous survey (conducted for the first Dutch *evidence-based* psoriasis guidelines, 2005). The literature search revealed the importance of specifying domains of treatment satisfaction [250, 251].

The questionnaire survey was comprised of 27, mainly multiple-choice questions on patient characteristics, disease duration and severity, prior and current treatments, as well as generic and specific treatment satisfaction. Questions about treatment satisfaction were answered on a 5-point scale: 1 = very dissatisfied and 5 = very satisfied. The group of "Satisfied patients" was defined as the group of patients with scores of 4 and 5 and the group of "Dissatisfied patients" as the group of patients with a score of 1. Patients with scores 2 and 3 were excluded from analysis.

For an extensive report on methodology, patient characteristics, data analysis, and results we refer to the complete Dutch S3-guidelines on the treatment of psoriasis 2011: http://www.huidarts.info/documents/uploaded_file.aspx?id=579. An international peer-reviewed publication is in preparation [252].

Conclusions

Following conclusions and recommendations are based on the research report.

EL: 3	1. About 1 out of 3 patients with psoriasis (32.4%) was satisfied with prior treatments. About 1 out of 14 patients (7.0%) was dissatisfied with prior treatments. 2a. About half of patients with psoriasis (53.8%) was satisfied with their current treatment. Patients with topical therapies were least satisfied, patients with systemic therapies were most satisfied. 2b. Patients receiving a topical therapy were least satisfied with effectiveness and convenience of treatment. Patients receiving phototherapy were least satisfied with effectiveness of treatment. Patients with systemic treatment were least satisfied with safety of treatment. 3. Patients value the effectiveness of treatment as the most important domain of satisfaction. The doctor-patient relationship was valued as important as treatment safety, and more important than convenience.

Recommendations on quality of life and treatment satisfaction

1. In dermatological practice, it is recommended to explicitly address the influence of psoriasis on quality of life by:
   a) Asking patients directly about their quality of life or by means of standardized questionnaires such as the DLQI or Skindex, if applicable and relevant.
   b) Modifying treatment and care, if necessary, based on current evidence.
2. In dermatological practice, it is recommended to explicitly address treatment satisfaction by:
   a) Asking patients directly about their treatment satisfaction (general as well as specific) regarding: 1) effectiveness, 2) safety, 3) convenience, 4) organization of treatment, 5) information about treatment, and 6) the doctor-patient relationship).
   b) Modifying treatment and care, if necessary, based on current evidence.
3. Additionally, it is recommended to professionals to determine norms or cut-off points for the interpretation of scores of satisfaction and dissatisfaction with treatment, based on evidence, suitability, and feasibility.

References

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496-509.
2. Gelfand JM, Stern RS, Nijsten T, et al. The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermtol 2005; 52: 23-26.
3. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999; 41:401-407.
4. Love TJ, Qureshi AA, Karlson EW, et al. Prevalence of the metabolic syndrome in psoriasis: results from the national health and nutrition examination survey, 2003-2006. Arch Dermatol. 2011; 147: 419-424.
5. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009; 129: 1339-1350.
6. Spuls PI, Tuut MK, van Everdingen JJ, et al. The practice guideline 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis'. Ned Tijdschr Geneeskd 2004; 148: 2121-2125.
7. Nast A, Kopp IB, Augustin M, et al. Evidence-based (S3) guidelines for the treatment of psoriasis vulgaris. J Dtsch Dermatol Ges 2007; 5 (Suppl. 3): 1-119.
8. Pathirana D, Omerod AD, Saiag P, et al. European S3 guideline on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009; 23 (Suppl. 2): 1-70.
9. Bijlsma JWJ, Hagemeijer JW, Bijl M, et al. The multidisciplinary practice guideline 'The responsible use of biologics'. Ned Tijdschr Geneeskd. 2011; 155: A3114.
10. van de Kerkhof PC, Murphy GM, Austad J, Ljungberg A, Cambazard F, Duvold LB. Psoriasis of the face and flexures. J Dermatolog Treat. 2007;18(6):351-360.
11. de Jager ME, de Jong EM, M van de Kerkhof PC, Seyger MM. Efficacy and safety of treatments for childhood psoriasis; A systematic literature review J Am Acad Dermatol. 2010;62:1013-1030.
12. Mason AR, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.:CD005028.
13. Ortonne JP, van de Kerkhof PC, Prinz JC, Bieber T, Lahfa M, Rubins A, et al. 0.3% Tacrolimus gel and 0.5% Tacrolimus cream show efficacy in mild to moderate plaque psoriasis: Results of a randomized, open-label, observer-blinded study. Acta Derm Venereol 2006;86(1):29-33.
14. Carroll CL, Clarke J, Camacho F, Balkrishnan R, Feldman SR. Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. Arch Dermatol 2005;141(1):43–46.
15. Monastirli A, Georgiou S, Pasmatzi E, Sakkis T, Badavanis G, Drainas D, et al. Calcipotriol plus short-contact dithranol:a novel topical combination therapy for chronic plaque psoriasis. Skin Pharmacol Appl Skin Physiol 2002;15(4):246–251.
16. Saraswat A, Agarwal R, Katare OP, Kaur I, Kumar B. A randomized, double-blind, vehicle-controlled study of a novel liposomal dithranol formulation in psoriasis. J Dermatol Treat 2007;18:40-45.
17. Gerritsen MJ, Boezeman JB, Elbers ME, van de Kerkhof PC. Dithranol embedded in crystalline monoglycerides combined with phototherapy (UVB): a new approach in the treatment of psoriasis. Skin Pharmacol Appl Skin Physiol 1998;11(3):133-139.
18. Prins M, Swinkels OQ, van de Kerkhof PC, van der Valk PG. The impact of the frequency of short contact dithranol treatment. Eur J Dermatol 2001;11(3):214-218.
19. Thune P und Brolund L. Short- and long-contact therapy using a new dithranol formulation in individually adjusted dosages in the management of psoriasis. Acta Derm Venereol Suppl (Stockh) 1992;172:28-29.
20. De Mare S, Calis N, den Hartog G, van Erp PE, van de Kerkhof PC. The relevance of salicylic acid in the treatment of plaque psoriasis with dithranol creams. Skin Pharmacol 1988;1(4):259-264.
21. Prins M, Swinkels OQ, Bouwhuis S, de Gast MJ, Bouwman-Boer Y, van der Valk PG, van de Kerkhof PC. Dithranol in a cream preparation:disperse or dissolve? Skin Pharmacol Appl Skin Physiol 2000;13(5):273-279.
22. Hutchinson PE, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 microg/g ointment in the treatment of plaque psoriasis:a comparison with short-contact dithranol. Dermatology 2000;201(2):139-145.
23. Mahrle G und Schulze HJ. The effect of initial external glucocorticoid administration on cignolin treatment of psoriasis. Z Hautkr 1990;65(3):282, 285–287.

24. Swinkels OQ, Prins M, Kucharekova M, de Boo T, Gerritsen MJ, van der Valk PG, et al. Combining lesional short-contact dithranol therapy of psoriasis with a potent topical corticosteroid. Br J Dermatol 2002;146(4):621-626.
25. van de Kerkhof PC, Green C, Hamberg KJ, Hutchinson PE, Jensen JK, Kidson P, et al. Safety and efficacy of combined high-dose treatment with calcipotriol ointment and solution in patients with psoriasis. Dermatology 2002;204(3):214–221.
26. Agrup G und Agdell J. A comparison between Antraderm stick (0.5% and 1%) and dithranol paste (0.125% and 0.25%) in the treatment of psoriasis. Br J Clin Pract. 1985;39(5):185-187.
27. Korte de J, van der Valk PG, Sprangers MA, Damstra RJ, Kunkeler AC, Lijnen RL, et al. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy:quality-of life outcomes of a randomized controlled trial of supervised treatment of psoriasis in a day-care setting. Br J Dermatol 2008;158:375-381.
28. Swinkels OQ, Prins M, Veenhuis RT, De Boo T, Gerritsen MJ, Van Der Wilt GJ, et al. Effectiveness and side effects of UVB-phototherapy, dithranol inpatient therapy and a care instruction programme of short contact dithranol in moderate to severe psoriasis. Eur J Dermatol. 2004;14(3):159-165.
29. van de Kerkhof PC, van der Valk PG, Swinkels OQ, Kucharekova M, de Rie MA, de Vries HJ, et al. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting. Br J Dermatol 2006 Oct;155(4):800-807.
30. Agarwal R, Saraswat A, Kaur I, Katare OP, Kumar B. A novel liposomal formulation of dithranol for psoriasis:preliminary results. J Dermatol. 2002;29(8):529-532.
31. Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. J Am Acad Dermatol 2003;48(1):48-54
32. Douglas WS, Poulin Y, Decroix J, Ortonne JP, Mrowietz U, Gulliver W, et al. A new calcipotriol/ betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol 2002;82(2):131-135.
33. Kaufmann R, Bibby AJ, Bissonnette R, Cambazard F, Chu AC, Decroix J,et al. A new calcipotriol/ betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. Dermatology 2002;205(4):389–393.
34. Weston WL, Fennessey PV, Morelli J, Schwab H, Mooney J, Samson C, et al. Comparison of hypothalamus-pituitary-adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. J Invest Dermatol 1988;90(4):532-535.
35. Bagatell F. Management of psoriasis: A clinical evaluation of the dermatological patch, Actiderm®, over a topical steroid. Adv Ther. 1988;5(6):291-296.
36. Gottlieb AB, Ford R, Spellman MC. The Efficacy and Tolerability of Clobetasol Propionate Foam 0.05% in the Treatment of Mild to Moderate Plaque-type Psoriasis of Nonscalp Regions. J Cutan Med Surg 2003;7(3):185-192.
37. Lowe N, Feldman SR, Sherer D, Weiss J, Shavin JS, Lin YL, et al. Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. J Dermatolog Treat 2005 Aug;16(3):158-164.
38. Decroix J, Pres H, Tsankov N, Poncet M, Arsonnaud S. Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. Cutis 2004;74(3):201-206.
39. Lebwohl M, Sherer D, Washenik K, Krueger GG, Menter A, Koo J, et al. A randomized, doubleblind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. Int J Dermatol 2002;41(5):269-274.
40. Lee CS, Koo J. The efficacy of three class I topical synthetic corticosteroids, fluocinonide 0.1% cream, clobetasol 0.05% cream and halobetasol 0.05% cream:a Scholtz-Dumas bioassay comparison. Journal of drugs in dermatology :JDD 2009;8:751-755.
41. Mazzotta A, Esposito M, Carboni I, Schipani C, Chimenti S. Clobetasol propionate foam 0.05% as a novel topical formulation for plaque-type and scalp psoriasis. J Dermatolog Treat 2007;18(2):84-87.

42. Thawornchaisit P, Harncharoen K. A comparative study of tar and betamethasone valerate in chronic plaque psoriasis:a study in Thailand. J Med Assoc Thai 2007 Oct;90(10):1997-2002.
43. Bagel J. LCD plus NB-UVB reduces time to improvement of psoriasis vs. NB-UVB alone. J Drugs Dermatol. 2009 Apr;8(4):351-357.
44. Belsito DV und Kechijian P. The role of tar in Goeckerman therapy. Arch Dermatol. 1982;118(5):319-321.
45. Frost P, Horwitz SN, Caputo RV, Berger SM. Tar gel-phototherapy for psoriasis. Combined therapy with suberythemogenic doses of fluorescent sunlamp ultraviolet radiation. Arch Dermatol 1979;115(7):840-846.
46. Camarasa JM, Ortonne JP, Dubertret L. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. J Dermatolog Treat. 2003;14(1):8–13.
47. Kragballe K, Noerrelund KL, Lui H, Ortonne JP, Wozel G, Uurasmaa T, et al. Efficacy of once daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. Br J Dermatol 2004;150(6):1167-1173.
48. Zhu X, Wang B, Zhao G, Gu J, Chen Z, Briantais P, et al. An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 microg/g ointment vs. calcipotriol 50 microg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol 2007 Apr;21(4):466-472.
49. Guenther LC, Poulin YP, Pariser DM. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. Clin Ther 2000;22(10):1225-1238.
50. Tabolli S, Alessandroni L, Didona B, Di PC, Gisondi P, Rota L, et al. A randomized controlled trial to evaluate short-term treatment with eosin vs. topical steroids in psoriasis. Clin Exp Dermatol 2009;34:304-308.
51. Guenther L, van de Kerkhof PC, Snellman E, Kragballe K, Chu AC, Tegner E, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris:a randomized, double-blind, vehicle-controlled clinical trial. Br J Dermatol 2002;147(2):316-323.
52. Ortonne JP, Kaufmann R, Lecha M, Goodfield M. Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris:a randomised, double-blind trial. Dermatology 2004;209(4):308-313.
53. Kragballe K, Austad J, Barnes L, Bibby A, de-la BM, Cambazard F, et al. Efficacy results of a 52-week, randomised, double-blind, safety study of a calcipotriol/betamethasone dipropionate two-compound product (Daivobet/Dovobet/Taclonex) in the treatment of psoriasis vulgaris. Dermatology 2006;213:319-326.
54. Peeters P, Ortonne JP, Sitbon R, Guignard E. Cost-effectiveness of once-daily treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol in the treatment of Psoriasis vulgaris. Dermatology 2005;211:139-145.
55. Saraceno R, Andreassi L, Ayala F, Bongiorno MR, Giannetti A, Lisi P, et al. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris:a randomized, multicentre, clinical trial. J Dermatol Treat 2007;18:361-365.
56. Hölzle E, Honigsmann H, Rocken M, Ghoreschi K, Lehmann P. Recommendations for phototherapy and photochemotherapy. J Dtsch Dermatol Ges. 2003 Dec;1(12):985-97.
57. Bonis B, Kemeny L, Dobozy A, Bor Z, Szabo G, Ignacz F. 308 nm UVB excimer laser for psoriasis. Lancet. 1997 Nov;350(9090):1522.
58. Halpern SM, Anstey AV, Dawe RS, Diffey BL, Farr PM, Ferguson J, et al. Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. Br J Dermatol 2000;142:22-31.
59. Dover JS, McEvoy MT, Rosen CF, Arndt KA, Stern RS. Are topical corticosteroids useful in phototherapy for psoriasis? J Am Acad Dermatol. 1989 May;20(5 Pt 1):748-54.
60. Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. Arch Dermatol. 1997 Dec;133(12):1514-22.
61. Orfanos CE, Steigleder GK, Pullmann H, Bloch PH. Oral retinoid and UVB radiation: a new, alternative treatment for psoriasis on an out-patient basis. Acta Derm Venereol. 1979;59(3):241-4.
62. Petrozzi JW. Topical steroids and UV radiation in psoriasis. Arch Dermatol. 1983 Mar;119(3):207-10.

63. Ramsay CA, Schwartz BE, Lowson D, Papp K, Bolduc A, Gilbert M. Calcipotriol cream combined with twice weekly broad-band UVB phototherapy: a safe, effective and UVB-sparing antipsoriatric combination treatment. The Canadian Calcipotriol and UVB Study Group. Dermatology. 2000;200(1):17-24.
64. Arnold WP, van Andel P, de Hoop D, de Jong-Tieben L, Visser-van Andel MA. Comparison of the effect of narrow-band ultraviolet B in the treatment of psoriasis after salt-water baths and after 8-methoxy-psoralen baths. Br J Dermatol. 2001 Aug;145(2):352-4.
65. Gordon PM, Diffey BL, Matthews JN, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. J Am Acad Dermatol. 1999 Nov; 41(5 Pt 1):728-32.
66. Markham T, Rogers S, Collins P. Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. Arch Dermatol. 2003 Mar;139(3):325-8.
67. Youssef RM, Mahgoub D, Mashaly HM, El-Nabarawy E, Samir N, El-Mofty M. Different narrowband UVB dosage regimens in dark skinned psoriatics: A preliminary study. Photodermatol Photoimmunol and Photomed. 24(5)(pp 256-259), 2008.
68. Grundmann-Kollmann M, Ludwig R, Zollner TM, Ochsendorf F, Thaci D, Boehncke WH, et al. Narrowband UVB and cream psoralen-UVA combination therapy for plaque-type psoriasis. J Am Acad Dermatol. 2004 May;50(5):734-9.
69. Leenutaphong V, Nimkulrat P, Sudtim S. Comparison of phototherapy two times and four times a week with low doses of narrow-band ultraviolet B in Asian patients with psoriasis. Photodermatol Photoimmunol Photomed. 2000 Oct;16(5):202-6.
70. Koek MB, Buskens E, van Weelden H, Steegmans PH, Bruijnzeel-Koomen CA, Sigurdsson V. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). BMJ 2009;338:b1542.
71. Cameron HY. Taking treatment to the patient: Development of a home TL-01 ultraviolet B phototherapy service. Br J Dermatol. 2002;147(5):957-65.
72. Hacker SM, Rasmussen JE. The effect of flash lamp-pulsed dye laser on psoriasis. Arch Dermatol. 1992 Jun;128(6):853-5.
73. Taibjee SM, Cheung ST, Laube S, Lanigan SW. Controlled study of excimer and pulsed dye lasers in the treatment of psoriasis. Br J Dermatol. 2005 Nov;153(5):960-6.
74. Trehan M, Taylor CR. Medium-dose 308-nm excimer laser for the treatment of psoriasis. J Am Acad Dermatol. 2002 Nov;47(5):701-8.
75. Goldinger SM, Dummer R, Schmid P, Vavricka MP, Burg G, Lauchli S. Excimer laser versus narrowband UVB (311 nm) in the treatment of psoriasis vulgaris. Dermatology. 2006;213(2):134-139.
76. Feldman SR, Mellen BG, Housman TS, Fitzpatrick RE, Geronemus RG, Friedman PM, et al. Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. J Am Acad Dermatol. 2002 Jun;46(6):900-6.
77. Han L, Somani AK, Huang Q, Fang X, Jin Y, Xiang LH, Zheng ZZ. Evaluation of 308-nm monochromatic excimer light in the treatment of psoriasis vulgaris and palmoplantar psoriasis. Photodermatology Photoimmunology and Photomedicine 2008;24(5):231-6.
78. Kollner K, Wimmershoff MB, Hintz C, Landthaler M, Hohenleutner U. Comparison of the 308-nm excimer laser and a 308-nm excimer lamp with 311-nm narrowband ultraviolet B in the treatment of psoriasis. Br J Dermatol. 2005 Apr;152(4):750-4.
79. Yones SS, Palmer RA, Garibaldinos TT, Hawk JLM. Randomized double-blind trial of the treatment of chronic plaque psoriasis: Efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. Arch Dermatol. 2006;142(7):836-842.
80. Caca-Biljanovska NG, V'Lckova-Laskoska MT. Management of guttate and generalized psoriasis vulgaris: prospective randomized study. Croat Med J. 2002 Dec;43(6):707-12.
81. Barth J, Dietz O, Heilmann S, Kadner H, Kraensel H, Meffert H, et al. Photochemotherapy by 8-methoxypsoralen and UVA in psoriasis vulgaris - clinical experiences in 5 dermatological departments of GDR (author's transl). Dermatol Monatsschr. 1978 Jun;164(6):401-7.
82. Berg M, Ros AM. Treatment of psoriasis with psoralens and ultraviolet A. A double-blind comparison of 8-methoxypsoralen and 5-methoxypsoralen. Photodermatol Photoimmunol Photomed. 1994 Oct;10 (5):217-20.

83. Buckley DA, Healy E, Rogers SA. Comparison of twice-weekly MPD-PUVA and three times-weekly skin typing-PUVA regimens for the treatment of psoriasis. Br J Dermatol. 1995 Sep;133(3):417-22.
84. Calzavara-Pinton P, Ortel B, Carlino A, Honigsmann H, De Panfilis GA. Reappraisal of the use of 5-methoxypsoralen in the therapy of psoriasis. Exp Dermatol. 1992 Jul;1(1):46-51.
85. Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. Br J Dermatol. 1992 Oct;127(4):392-5.
86. Cooper EJ, Herd RM, Priestley GC, Hunter JA. A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. Clin Exp Dermatol. 2000 Mar;25(2):111-4.
87. Diette KM, Momtaz TK, Stern RS, Arndt KA, Parrish JA. Psoralens and UVA and UV-B twice weekly for the treatment of psoriasis. Arch Dermatol. 1984 Sep;120(9):1169-73.
88. Hanke CW, Steck WD, Roenigk Jr. HH. Combination therapy for psoriasis. Psoralens plus long-wave ultraviolet radiation with betamethasone valerate. Arch Dermatol. 1979 Sep;115(9):1074-7.
89. Khurshid K, Haroon TS, Hussain I, Pal SS, Jahangir M, Zaman T. Psoralenultraviolet A therapy vs. psoralen-ultraviolet B therapy in the treatment of plaque-type psoriasis: our experience with fitzpatrick skin type IV. Int J Dermatol. 2000 Nov;39(11):865-7.
90. Kirby B, Buckley DA, Rogers S. Large increments in psoralen-ultraviolet A (PUVA) therapy are unsuitable for fair-skinned individuals with psoriasis. Br J Dermatol. 1999 Apr;140 (4):661-6.
91. Park YK, Kim HJ, Koh YJ. Combination of photochemotherapy (PUVA) and ultraviolet B (UVB) in the treatment of psoriasis vulgaris. J Dermatol. 1988 Feb;15(1):68-71.
92. Parker S, Coburn P, Lawrence C. Marks J, Shuster S. A randomized double-blind comparison of PUVA-etretinate and PUVA-placebo in the treatment of chronic plaque psoriasis. Br J Dermatol. 1984 Feb;110(2):215-20.
93. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. N Engl J Med. 1974 Dec 5;291(23):1207-11.
94. Rogers S, Marks J, Shuster S, Vella Briffa DV, Warin A, Greaves M. Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis. Lancet. 1979 Mar 3;1(8114):455-8.
95. Vella Briffa D, Rogers S, Greaves MW, Marks J, Shuster S, Warin AP. A randomized, controlled clinical trial comparing photochemotherapy with dithranol in the initial treatment of chronic plaque psoriasis. Clin Exp Dermatol. 1978 Dec;3(4):339-47.
96. El-Mofty M, El Weshahy H, Youssef R, Abdel-Halim M, Mashaly H, El Hawary M. A comparative study of different treatment frequencies of psoralen and ultraviolet A in psoriatic patients with darker skin types (randomized-controlled study). Photodermatology Photoimmunology and Photomedicine. 2008; 24(1):38-42.
97. Henseler T, Wolff K, Honigsmann H, Christophers E. Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. Lancet. 1981 Apr 18;1(8225):853-7.
98. Saurat JH, Geiger JM, Amblard P, Beani JC, Boulanger A, Claudy A, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica. 1988;177(4):218-24.
99. Carlin CS, Callis KP, Krueger GG. Efficacy of acitretin and commercial tanning bed therapy for psoriasis. Arch Dermatol. 2003 Apr;139(4):436-42.
100. Lauharanta J, Geiger JM. A double-blind comparison of acitretin and etretinate in combination with bath PUVA in the treatment of extensive psoriasis. Br J Dermatol. 1989 Jul;12 (1):107-12.
101. Flytstrom I, Stenberg B, Svensson A, Bergbrant I-M. Methotrexate vs ciclosporin in psoriasis: effectiveness, quality of life and safety. Br J Dermatol 2008;158:116-121.
102. Ranjan N, Sharma NL, Shanker V, Mahajan VK, Tegta GR. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis:a comparative study. J Dermatol Treat 2007;18(5):295-300.
103. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558-566.

104. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003 Aug 14;349(7):658-665.
105. Akhyani M, Chams-Davatchi C, Hemami MR, Fateh S. Efficacy and safety of mycophenolate mofetil vs methotrexate for the treatment of chronic plaque psoriasis. J Eur Acad Dermatol Venereol 2010 Dec;24(12):1447-1451.
106. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy; a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88:1242-1247.
107. Koo J. A randomized, double-blind study comparing the efficacy, safety and optimal dose of two formulations of cyclosporin, Neoral and Sandimmun, in patients with severe psoriasis. OLP302 Study Group. Br J Dermatol. 1998;139:88-95.
108. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaquetype psoriasis. Results of a multidose, double-blind trial. N Engl J Med. 1991 31;324:277-284.
109. Nijsten TE, Stern RS. Genital squamous cell carcinoma in men treated by photochemotherapy. A cancer registry-based study from 1978 to 1998. Br J Dermatol. 2002;147:184-5; author reply 185-186.
110. Yuan J, Zhou J, Chen BC, Zhang X, Zhou HM, Du DF, et al. Magnesium supplementation prevents chronic cyclosporine nephrotoxicity via adjusting nitric oxide synthase activity. Transplant Proc. 2005;37:1892-1895.
111. Kragballe K, Jansen CT, Geiger JM, Bjerke JR, Falk ES, Gip L, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. Acta Derm Venereol. 1989;69(1):35-40.
112. Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. J Am Acad Dermatol. 1989 Jun;20(6):1088-1093.
113. van de Kerkhof PC, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, et al. The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998 Jan;138(1):84-89.
114. Gronhoj Larsen F, Steinkjer B, Jakobsen P, Hjorter A, Brockhoff PB, Nielsen-Kudsk F. Acitretin is converted to etretinate only during concomitant alcohol intake. Br J Dermatol. 2000 Dec;143(6):1164-1169.
115. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol. 1994 Jun;30(6):977-981.
116. Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, et al. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. Dermatology. 2002;205(1):46-53.
117. Nugteren-Huying WM, Schroeff JG van der, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 1990;22:311-312.
118. Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992 Nov;27(5 Pt 1):769-771.
119. Nieboer C, Hoop D de, Langendijk PNJ, Loenen AC van, Gubbels J. Fumaric acid therapy in psoriasis; A double-blind comparison between fumaric acid compound therapy and monotherapy with dimethyl-fumaric acid ester. Dermatologica 1990;181:22-27.
120. Altmeyer P, Hartwig R, Matthes U. Efficacy and safety profile of fumaric acid esters in oral longterm therapy with severe treatment refractory psoriasis vulgaris. A study of 83 patients. Hautarzt 1996;47:190-196.
121. Bayard W, Hunziker T, Krebs A, Speiser P, Joshi R. Peroral long-term treatment of psoriasis using fumaric acid derivatives. Hautarzt 1987;38:279-285.
122. Litjens NH, Nibbering PH, Barrois AJ, Zomerdijk TP, van den Oudenrijn AC, Noz KC, et al. Beneficial effects of fumarate therapy in psoriasis vulgaris patients coincide with downregulation of type 1 cytokines. Br J Dermatol 2003;148:444-451.
123. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. J Dermatolog Treat. 2004;15:23-26.

124. Mrowietz U, Christophers E, Altmeyer P, for the German Fumaric Acid Ester Consensus Conference. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. Br J Dermatol 1999;141:424-429.
125. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: an European consensus. Arch Dermatol Res. 2011 Jan;303(1):1-10.
126. Lecluse LL, de Groot M, Bos JD, Spuls PI. Experience with biologics for psoriasis in daily practice: switching is worth a try. Br J Dermatol. 2009:161(4):948-951.
127. van Lümig PP, Lecluse LL, Driessen RJ, Spuls PI, Boezeman JB, van de Kerkhof PC, et al. Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept. Br J Dermatol. 2010 Oct;163(4):838-846.
128. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet. 2001 Sep 29;358(9287):1042-1045.
129. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. J Invest Dermatol. 2003 Aug;121(2):252-258.
130. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol. 2005 Mar;124(3):505-513.
131. Paul CF, Gourraud PA. Cancer risk evaluation in psoriasis: in search of the Holy Grail? J Invest Dermatol. 2009 Nov;129(11):2547-2549.
132. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, doubleblind, placebo-controlled trial (PHOENIX 2). Lancet 2008; 371: 1675-1684.
133. van Lümig PP, Driessen RJ, Roelofs-Thijssen MA, Boezeman JB, van de Kerkhof PC, de Jong EM. Relevance of laboratory investigations in monitoring patients with psoriasis on etanercept or adalimumab. Br J Dermatol. 2011 Aug;165(2):375-382.
134. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011 Aug 24;306(8):864-871.
135. Furst DE.The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum. 2010 Apr;39(5):327-346.
136. Montagna GL, Malesci D, Buono R, Valentini G. Asthenoazoospermia in patients receiving antitumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005 Nov;64(11):1667.
137. Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P. Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis. 2005 Apr;11(4):395-399.
138. Paschou S, Voulgari PV, Vrabie IG, Saougou IG, Drosos AA. Fertility and reproduction in male patients with ankylosing spondylitis treated with infliximab. J Rheumatol. 2009 Feb;36(2):351-354.
139. Simister NE. Placental transport of immunoglobulin G. Vaccine. 2003 Jul 28;21(24):3365-3369.
140. Krieckaert CL, Bartelds GM, Lems WF et al. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. Arthritis Res Ther 2010; 12: 217.
141. de Vries MK, van der Horst-Bruinsma IE, Nurmohamed MT et al. Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis (AS). Ann Rheum Dis 2009;68:531-535.
142. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol 2005;153:486-497.
143. Altena van R, Arend SM, Bossink AWJ, Erkens CGM, van Kuijk SJTh, van Leth F et al. Richtlijn: Interferon Gamma Release Assays bij de diagnostiek van tuberculose 2010. www.kncvtbc.nl . 18-4-2011.
144. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 2009;60:1884-1894.
145. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al.Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006;55(4):598-606.

146. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol 2008;58(1):106-15.
147. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003 Dec;139(12):1627-1632.
148. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003 Nov 20;349(21):2014-2022.
149. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebocontrolled randomised phase III trial. Lancet. 2006 Jan 7;367(9504):29-35.
150. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005 Jun;152(6):1304-1312.
151. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64 (8):1150-1157.
152. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. Intermittent infliximab maintenance regimens over 1 year in the treatment of moderate to severe plaque psoriasis. J Am Acad Dermatol 2007;56(1):31.e1-15.
153. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005;366(9494): 1367-1374.
154. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004;51(4):534-542.
155. Leonardi C, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (phoenix 1). The Lancet. 2008;371:1665-1674.
156. Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R. Responses to ustekinumab in the anti TNF agent-naïve vs. anti-TNF agent-exposed patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2011 Sep;25(9):1037-40.
157. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol. 2011 Jan 11.
158. de Groot M, Appelman M, Spuls PI, De Rie MA, Bos JD. Initial experience with routine administration of etanercept in psoriasis. Br J Dermatol. 2006;155:808-14.
159. Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. Arch Dermatol. 2010;146(2):127-32.
160. Woolacott N, Vergel BY, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006;10(31):iii-iv, xiii-xvi,1-239.
161. Fauéré S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. J Eur Acad Dermatol. 2005;19:2-6.
162. Dubertret L, Mrowietz U, Ranki A, van de Kerkhof PC, Chimenti T, Lotti T, et al. On behalf of the EUROPSO patient survey. European patient perspectives on the impact at psoriasis: the EUROPSO patient membership survey. Br J Dermatol 2006;155:729-736.
163. van de Kerkhof PC, de Hoop D, de Korte J, Cobelens SA, Kuipers MV. Patient compliance and disease management in the treatment of psoriasis in the Netherlands. Dermatology 2000;200:292-299.
164. Farber EM, Bright RD, Nall ML. Psoriasis: a questionnaire survey of 2,144 patients. Arch Dermatol 1968;98:248-259.
165. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. Dermatologica 1974;148:1-18.
166. Wang G, Li C, Gao T, Liu Y. Clinical analysis of 48 cases of inverse psoriasis: a hospital based study. Eur J Dermatol 2005;15(3):176-178.

167. Nanda A, Kaur S, Kaur I, Kumar B. Childhood psoriasis: an epidemiological survey of 112 patients. Pediatr Dermatol 1990;7:19-21.
168. Puissant A. Psoriasis in children under the age of ten: a study of 100 observations. Gazz Sanitaria 1970;19:191-198.
169. Nyfors A, Lemholt K. Psoriasis in children: a short review and a survey of 245 patients. Br J Dermatol 1975;92:437-448.
170. Park JY, Rim JH, Choe YB, Youn YI. Facial psoriasis: comparison of patients with and without facial involvement. J Am Acad Dermatol 2004;50:582-584.
171. Woo SM, Choi JW, Yoon HS, Jo SJ, Youn JI. Classification of facial psoriasis based on the distributions of facial lesions. J Am Acad Dermatol 2008;58:959-963.
172. Rosenberg EW, Noah PW, Skinner RB, van der Zwaag R, Weest SK, Browder JF. Microbial association of 167 patients with psoriasis. Acta Derm Venereol 1989;69:72-75.
173. Lane CG, Craford GM. Psoriasis: a statistical study of 231 cases. Arch Dermatol 1937;35:1051-61.
174. Lomholt G. Influence of sun- and sea-bathing. In: Psoriasis: Prevalence, Spontaneous Course and Genetics: a Census Study on the Prevalence of Skin Diseases on the Faroe Islands. Copenhagen: G.E.C. GAD 1963;113-4.
175. Braun-Falco O, Burg G, Farber EM. Psoriasis: eine Fragebogenstudie bei 536 Patienten. Munch. Med. Wochenschr. 1972;114:1105-10.
176. Leigheb G, Gallus D, Spano G. Treatment with psoriasis with an antiseptic combination, in a doubleblind comparison versus eosin. G Ital Dermatol Venereol 2000;135:107-114.
177. Doering HF. Therapy and etiology of sebopsoriasis. Z Hautkr 1985;6:1940-1950.
178. Faergemann J. Treatment of sebopsoriasis with itraconazole. Mykoses 1985;28:612-618.
179. Heller G. Niedrig konzentriertes Dithranol bei Psoriasis des Gesichtes. Dermatol Monatschr 1989;175:35-39.
180. Kreuter A, Sommer A, Hyun J, Brautigam M, Brockmeyer NH, Altmeyer P, et al. 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a doubleblind, randomized controlled study. Arch Dermatol. 2006;142:1138-1143.
181. Lebwohl MG, Tan MH, Meador SL, Singer G. Limited application of fluticasone propionate ointment 0,005% in patients with psoriasis of the face and intertriginous areas. J Am Acad Dermatol 2001;44:77- 82.
182. Liao YH, Chiu HC, Tseng YS, Tsai EF. Comparison of cutaneous tolerance and efficacy of calcitriol 3 ug/g ointment and tacrolimus 0,3 mg/g ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. British Journal of Dermatology 2007;157:1005–1012.
183. Ortonne JP, Humbert P, Nicolas JF, Tsankov N, Tonev SD, Janin A, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3mcg g-1 ointment and calcipotriol 50 mcg g-1 ointment on chronic plaque psoriasis localized in facial, hairline, retroauriculair or flexural areas. Br J Dermatol 2003;148:326-333.
184. Duweb GA, Eldebani S, Alhaddar J. Calcipotriol cream in the treatment of flexural psoriasis. Int J Tissue React 2003; 25:127-130.
185. Kienbaum S, Lehmann P, Ruzicka T. Topical Calcipotriol in the treatment of intertriginous psoriasis. Br J Dermatol 1996; 135:647-650.
186. Langer A, Stapor V, Verjans H, Elzerman J. Calcitriol ointment in the treatment of facial, hairline and retroauricular chronic plaque psoriasis. J Dermatol Treat 1996;7(Suppl.l):S15-S18.
187. Lebwohl M, Freeman AK, Chapman MS, Feldman S, Hartle JE, Henning A, et al. Tacrolimus ointment is effective for facial and intertriginous psoriasis. J Am Acad Dermatol 2004;51:723-730.
188. Gribetz C, Ling M, Lebwohl M, Pariser D, Draelos Z, Gottlieb AB, et al. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. J Am Acad Dermatol 2004;51:731-738.
189. Kleyn CE, Woodcock D, Sharpe GR. The efficacy of 0.1% tacrolimus ointment compared with clobetasonebutyrate 0.05% ointment in patients with facial flexural or genital psoriasis. Br J Dermatol 2005;153(Suppl.1):33.
190. Zanchi M, Favot F, Bizarrini M, Piai M, Donini M, Sedona P. Botulinum toxin type-A for the treatment of inverse psoriasis. JEADV 2008;22:431–436.

191. Herz G, Blum G, Yawalkar S. Halobetasol propionate cream by day and halobetasol propionate ointment at night for the treatment of pediatric patients with chronic, localized plaque psoriasis and atopic dermatitis. J Am Acad Dermatol 1991;25:1166-1169.
192. Kimball AB, Gold MH, Zib B, Davis MW. Clobetasol propionate emulsion formulation foam 0.05%; review of phase II open-label and phase III randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. J Am Acad Dermatol 2008;59:448-454.
193. Feicht G. Psoriasis pustulosa in children. H+G-Zeitschrift-fur-Hautkrankheiten 1982;57:1694-1696.
194. Oranje AP, Marcoux D, Svensson A, Prendiville J, Krafchik B, Toole J, et al. Topical calcipotriol in childhood psoriasis. J Am Acad Dermatol 1997;36:203-208.
195. Perez A, Chen TC, Turner A, Holick MF. Pilot study of topical calcitriol (1, 25-dihydroxyvitamin D3) for treating psoriasis in children. Arch Dermatol 1995;131:961-962.
196. Brune A, Miller DW, Lin P, Cotrim-Russi D, Paller AS. Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. Pediatr Dermatol 2007;24:76-80.
197. Steele JA, Choi C, Kwong PC. Topical tacrolimus in the treatment of inverse psoriasis in children. J Am Acad Dermatol 2005;53:713-716.
198. Amichai B. Psoriasis of the glans penis in a child successfully treated with Elidel (pimecrolimus) cream. J Eur Acad Dermatol Venereol 2004;18:742-743.
199. Mansouri P, Farshi S. Pimecrolimus 1 percent cream in the treatment of psoriasis in a child. Dermatol Online J 2006;12:7.
200. Zvulunov A, Anisfeld A, Metzker A. Efficacy of short-contact therapy with dithranol in childhood psoriasis. Int J Dermatol 1994;33:808-810.
201. Guerrier CJ, Porter DI. An open assessment of 0.1% dithranol in a 17% urea base ('Psoradrate' 0.1%) in the treatment of psoriasis of children. Curr Med Res Opin 1983;8:446-450.
202. Schubert B, Seitz CS, Brocker EB, Hamm H. Exanthematous infantile psoriasis. J Dtsch Dermatol Ges 2007;5:680-682.
203. al-Fouzan AS, Nanda A. UVB phototherapy in childhood psoriasis. Pediatr Dermatol 1995;12:66.
204. Jain VK, Aggarwal K, Jain K, Bansal A. Narrow-band UV-B phototherapy in childhood psoriasis. Int J Dermatol 2007;46:320-322.
205. Jury CS, McHenry P, Burden AD, Lever R, Bilsland D. Narrowband ultraviolet B (UVB) phototherapy in children. Clin Exp Dermatol 2006;31:196-199.
206. Pasic A, Ceovic R, Lipozencic J, Husar K, Susic SM, Skerlev M, et al. Phototherapy in pediatric patients. Pediatr Dermatol 2003;20:71-77.
207. Tay YK, Morelli JG, Weston WL. Experience with UVB phototherapy in children. Pediatr Dermatol 1996;13:406-409.
208. Kim MK, Ko YH, Yeo UC, Kim YG, Oh HY. Psoriasis and glomerulonephritis. Clin Exp Dermatol 1998;23:295-296.
209. Thappa DM, Laxmisha C. Suit PUVA as an effective and safe modality of treatment in guttate psoriasis. J Eur Acad Dermatol Venereol 2006;20:1146-1147.
210. Patrizi A, Costa AM, Fiorillo L, Neri I. Perianal streptococcal dermatitis associated with guttate psoriasis and/or balanoposthitis; a study of five cases. Pediatr Dermatol 1994;11:168-171.
211. Pacifico L. Acute guttate psoriasis after streptococcal scarlet fever [2]. Pediatric-Dermatology 1993;10:388-389.
212. Rosinska D, Wolska H, Jablonska S, Konca I. Etretinate in severe psoriasis of children. Pediatr Dermatol 1988;5:266-272.
213. van de Kerkhof PC. Generalized pustular psoriasis in a child. Dermatologica 1985; 170:244-248.
214. Pavicic Z, Kmet-Vizitin P, Kansky A. Etretinate in treating juvenile generalized pustular psoriasis. In; Farber EM, Cox AJ, editors. Proceedings of the 4th international symposium on psoriasis, Stanford University.Stanford; University Press; 1986. p. 467.
215. Kim BS, Shin S, Youn JI, Lee YS. Treatment of erythrodermic psoriasis with etretinate. Annals-of-Dermatology 1991;3:107-111.
216. van der Rhee HJ, van Gelderen HH, Polano MK. Is the use of Ro 10-9359 (Tigason) in children justified? Acta Derm Venereol 1980;60:274-275.

217. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. J Am Acad Dermatol 2003;49:171-82.
218. Mahe E, Bodemer C, Pruszkowski A, Teillac-Hamel D, de PY. Cyclosporine in childhood psoriasis. Arch Dermatol 2001;137:1532-1533.
219. Kilic SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim I. Low dose cyclosporin A treatment in generalized pustular psoriasis. Pediatr Dermatol 2001;18:246-248.
220. Alli N, Gungor E, Karakayali G, Lenk N, Artuz F. The use of cyclosporin in a child with generalized pustular psoriasis. Br J Dermatol 1998;139:754-755.
221. Torchia D, Terranova M, Fabbri P. Photosensitive psoriasis in a vitiligo patient. J Dermatol 2006;33:880-883.
222. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, et al. Cyclosporin for severe childhood atopic dermatitis; short course versus continuous therapy. Br J Dermatol 2000;142:52-8.
223. Berth-Jones J. The use of ciclosporin in psoriasis. J Dermatolog Treat 2005;16:258-77.
224. Collin B, Ogboli M, Moss C. Methotrexate therapy in 10 children with severe plaque psoriasis; P-29. British Journal of Dermatology 2006;155(Suppl 1):33.
225. Kaur I, Dogra S, De D, Kanwar AJ. Systemic methotrexate treatment in childhood psoriasis; further experience in 24 children from India. Pediatr Dermatol 2008;25:184-188.
226. Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. Pediatr Dermatol 1994;11:271-273.
227. Kalla G, Goyal AM. Juvenile generalized pustular psoriasis. Pediatr Dermatol 1996;13:45-46.
228. Dogra S, Handa S, Kanwar AJ. Methotrexate in severe childhood psoriasis. Pediatr Dermatol 2004;21:283-284.
229. Dogra S, Kumaran MS, Handa S, Kanwar AJ. Methotrexate for generalized pustular psoriasis in a 2-year-old child. Pediatr Dermatol 2005;22:85-86.
230. Ivker RA, Grin-Jorgensen CM, Vega VK, Hoss DM, Grant-Kels JM. Infantile generalized pustular psoriasis associated with lytic lesions of the bone. Pediatr Dermatol 1993;10:277-282.
231. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58:1496-504.
232. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med 2008 17;358:241-251.
233. Pereira TM, Vieira AP, Fernandes JC, Antunes H, Basto AS. Anti-TNF-alpha therapy in childhood pustular psoriasis. Dermatology 2006;213:350-352.
234. Farnsworth NN, George SJ, Hsu S. Successful use of infliximab following a failed course of etanercept in a pediatric patient. Dermatol Online J 2005;11:11.
235. Menter MA, Cush JM. Successful treatment of pediatric psoriasis with infliximab. Pediatr Dermatol 2004;21:87-88.
236. Weishaupt C, Metze D, Luger TA, Stander S. Treatment of pustular psoriasis with infliximab. J Dtsch Dermatol Ges 2007;5:397-399.
237. Lin YK, Yen HR, Wong WR, Yang SH, Pang JH. Successful treatment of pediatric psoriasis with Indigo naturalis composite ointment. Pediatr Dermatol 2006;23:507-510.
238. Pahlajani N, Katz BJ, Lozano AM, Murphy F, Gottlieb A. Comparison of the efficacy and safety of the 308 nm excimer laser for the treatment of localized psoriasis in adults and in children; a pilot study. Pediatr Dermatol 2005;22:161-165.
239. Diluvio L, Campione E, Paterno EJ, Mordenti C, El HM, Chimenti S. Childhood nail psoriasis; a useful treatment with tazarotene 0.05%. Pediatr Dermatol 2007;24:332-333.
240. Michalowski R, Olejnicka Z, Kozak S, Urban J. Studies on the therapeutic effect of Wratizolin in selected dermatoses. Arch Immunol Ther Exp (Warsz) 1983;31:649-654.
241. Gunther CH. Successive use of fumaric acid esters for the treatment of psoriasis vulgaris in a 14-year old patient. Haut- 2004;15:28-30.
242. Yu HJ, Park JW, Park JM, Hwang DK, Park YW. A case of childhood generalized pustular psoriasis treated with dapsone. J Dermatol 2001;28:316-319.
243. Fernandes-El, Ferreira-CT, Da-Silveira-TR, Cestari-TF. Pustular psoriasis and Crohn's disease; Case report. Anais-Brasileiros-de-Dermatologia 2000;75:57-64.

244. Tsuge I, Fujii H, Andou Y, Katayama I, Kajita M, Haga Y, et al. A case of infantile febrile psoriasiform dermatitis. Pediatr Dermatol 1995;12:28-34.
245. McMillin BD, Maddern BR, Graham WR. A role for tonsillectomy in the treatment of psoriasis? Ear Nose Throat J 1999;78:155-158.
246. Hone SW, Donnelly MJ, Powell F, Blayney AW. Clearance of recalcitrant psoriasis after tonsillectomy. Clin Otolaryngol Allied Sci 1996;21:546-547.
247. Wahba A, Cohen H. Therapeutic trials with oral colchicine in psoriasis. Acta Derm Venereol 1980;60:515-520.
248. Zachariae H, Kragballe K, Herlin T. Colchicine in generalized pustular psoriasis; clinical response and antibody-dependent cytotoxicity by monocytes and neutrophils. Arch Dermatol Res 1982;274:327-333.
249. Food and Drug Administration (2009). Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Ref Type: Report.
250. Atkinson MJ, Sinha A, Hass SL et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004;2:12.
251. Ruiz MA, Pardo A, Rejas J, Soto J,. Vallisante F, Aranguren JL. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). Value Health 2008;11:913-926.
252. van Cranenburgh OD, de Korte J, Sprangers MA, de Rie MA, Smets EM. Satisfaction with treatment among patients with psoriasis: a web-based survey study. Br J Dermatol. 2013 Aug;169(2):398-405.

11

Combined use of systemic agents for psoriasis: a systematic review

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Abstract

Importance: Combined use of systemic agents may be necessary to achieve disease control in therapy-resistant patients. However, to our knowledge, an overview of evidence, including quality assessments, is not yet available, and no guidance on monitoring, contraindications, and interactions exists.

Objective: To summarize and critically appraise the evidence on efficacy and safety of combination therapy with systemic agents in plaque-type psoriasis.

Evidence review: Through March 2013, an electronic search limited to randomized clinical trials was performed in MEDLINE, EMBASE, The Cochrane Library and ongoing trial registers. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach.

Findings: The initial search retrieved 2583 records, of which 17 met the inclusion criteria. Most studies favored combination therapy, albeit with low significance and low quality of evidence. Etanercept plus methotrexate was the only combination therapy investigated with an adequate sample size (n = 478). In the short term, this combination had superior efficacy with a moderate quality of evidence compared with etanercept monotherapy (Psoriasis Area and Severity Index 75; relative risk, 1.28: 95% CI, 1.14-1.45). Although this finding coincided with an increase in adverse events (relative risk, 1.25; 95% CI, 1.10-1.42), the overall safety profile remained acceptable.

Conclusions and Relevance: This systematic review provides a comprehensive overview on the validity of different systemic combination therapies. For most combinations, insufficient evidence is available. Initial results indicate that combined therapy with etanercept plus methotrexate may be beneficial in patients that are therapy resistant under intensive follow-up. Dose reductions should be taken into account to minimize adverse events.

Introduction

Combination therapy with systemic agents is used in clinical practice because it may enhance efficacy, accelerate the onset of remission, and reduce adverse events (AEs) by permitting dose reductions. However, it may also induce more, unknown, and other AEs, and no guidance is available on monitoring, contraindications, and interactions. Although several systematic reviews[1-3] provide a summary of studies that report on combination therapy with systemic agents, no risk of bias assessments of the individual studies were provided. The National Clinical Guideline Centre performed quality assessments on combination therapy with retinoids and phototherapy, but no other combination therapies with systemic agents were analyzed.[4] Recommendations in clinical guidelines on combination therapy, if any, are frequently based on few randomized clinical trials (RCTs) or observational studies, case reports, and expert opinion.[5-8] We conducted a systematic review of RCTs on the efficacy and safety of combination therapy with systemic agents for plaque-type psoriasis. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[9]

Methods

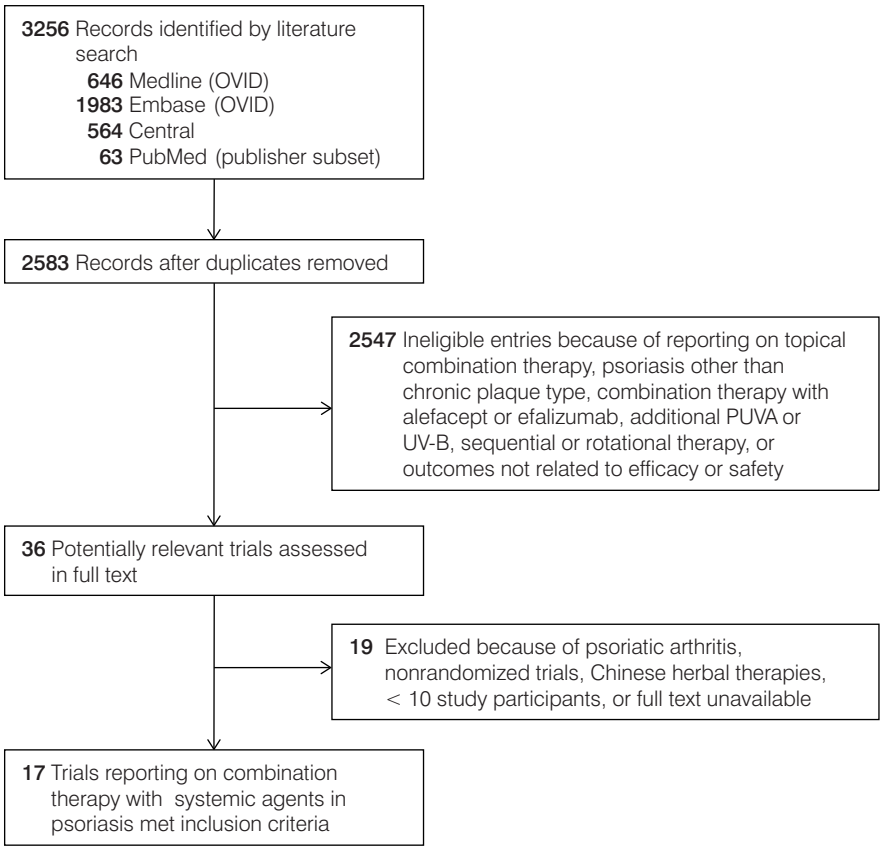
Search method

A medical librarian (J.L.) performed a literature search to identify RCTs of combination therapy with systemic agents in plaque-type psoriasis. Through March 2013, MEDLINE (OVID, from 1948), EMBASE (OVID, from 1980), Cochrane Central Register of Controlled Trials (CENTRAL, from inception), PubMed (the publisher subset fraction, which contains publications ahead of print that are not yet included in OVID MEDLINE) and ongoing trial registers (http://clinicaltrials.gov/) were searched with no language restrictions. The latest update was March 2013. Animal studies were safely excluded by using double negation. The search strategies consisted of searching for the keywords *psoriasis* and *combination therapy* in Medical Subject Headings and titles and abstracts. In MEDLINE and EMBASE, the topic search was combined with a methodological filter adapted from the Cochrane Central Register of Controlled Trials to identify RCTs and clinical controlled trials (eFigure 1 in the Supplement details the entire MEDLINE search).[10-11] The search included an iterative process for each database to refine the search strategy through incorporation of new search terms as new relevant citations were identified (i.e., by checking reference lists and citing articles using ISI Web of Science [Thomson Reuters]). Reference Manager software, version 12.0 (Thomson Reuters) was used to deduplicate, store, and analyze the search results.

Selection criteria

The RCTs (N >10) that reported on the efficacy and safety of combination therapy with systemic agents compared with systemic monotherapy or another systemic combination therapy in plaque-type psoriasis were included. Studies that reported on other types of psoriasis, sequential or rotational therapies, and unclear (i.e., Chinese herbal) combination therapies were excluded and studies that reported on alefacept and efalizumab were excluded because these treatment modalities are no longer available. Furthermore, studies that reported on phototherapy plus acitretin were excluded because, for this type of combination therapy, an overview of RCT evidence according to the GRADE approach already exists[4] (Figure 1).

Figure 1 Search strategy and retrieved articles



Study selection

Titles and abstracts from the electronic searches were screened, and full manuscripts of all citations that met the predefined selection criteria were obtained. Subsequently, full articles were examined for inclusion or exclusion. The selection was independently performed by two reviewers (C.B. and J.Z.). Any disagreements were resolved by consensus or arbitration of a third reviewer (P.I.S.).

Data extraction

Information on study reference, year of publication, study design, number of patients, baseline disease severity, treatment regimen, duration of combination therapy, and follow-up were extracted. Critical and important outcomes were selected to assess the quality of evidence. Critical outcomes were defined as the proportion of patients who attained Psoriasis Area and Severity Index (PASI) 75, PASI 90, and a Physician Global Assessment (PGA) of clear or almost clear; withdrawals because of AEs; proportion of patients who experienced serious adverse events (SAEs); and mean change in Dermatology Life Quality Index (DLQI). Important outcomes were defined as number of withdrawals because of lack of efficacy, proportion of patients with AEs, mean change in PASI (0-72, 0-16 and 0-18), mean time to clearance, and mean time to relapse. Only results from intention-to-treat (ITT) analysis were used if both ITT and per-protocol data were available. Efficacy outcomes were divided into 2 groups based on duration of combination therapy: ≤ 12 weeks or >12 weeks. The number of events and total number of participants in each group were used for extracting dichotomous variables. Means and standard deviations (SDs) were used for extracting continuous variables.

Assessment and Evaluation of the Quality of Evidence

The risk of bias in the individual studies was assessed in duplicate (C.B. and J.Z.) using the Cochrane Risk of Bias tool.[10] Accordingly, we graded sequence generation, allocation concealment, blinding of caregivers and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias as low, unclear or high risk of bias. Subsequently, an overall assessment for each RCT was conducted using the same three criteria. The quality of evidence for each outcome (body of evidence) was assessed according to the GRADE approach[9] by using the GRADE profiler software, version 3.2.2.[12]

Statistics

The threshold for statistical significance was set at $P<0.05$ for effect sizes. Mean difference (MD) with 95% confidence interval (95% CI) was calculated for continuous variables. An imputed correlation coefficient of 0.70 was used to calculate the change-from-baseline SDs. The value of the correlation coefficient could not be

imputed from another study and was therefore hypothesized.[10] Relative risk or risk ratio (RR) with a 95% CI was used to calculate the effects for dichotomous outcomes. The Optimal Information Size (OIS) was calculated using a relative risk ratio (RRR) of 25% and assuming an α of 0.05 and a of 0.2 if consideration of 95% CIs alone suggested a robust effect, but the total sample size and the number of events were small.[13] Meta-analysis to calculate a weighted treatment effect across trials and a funnel plot to detect publication and other reporting biases by plotting could not be performed because of a lack of more than one trial of the same comparison or absence of similar treatment regimens.

Results

Trial Characteristics

The search identified 2583 references to RCTs that investigated combination therapy with systemic agents for psoriasis. Thirty-six references were selected for full-text examination, and 17 RCTs with a total of 1071 participants (median, 71 participants; range, 10-478 participants) were included (Figure 1). The characteristics of included studies and outcome measures used for analysis are listed in Table 1.

Quality of evidence of the included studies

Assessment of the risk of bias of the individual studies resulted in low risk for 3 trials [14-16] intermediate risk for 5 trials[17-21] and high risk for 9 trials[22-30].Methodological limitations were unclear allocation concealment (14/14 trials), inadequate or partial blinding (14/14), unclear baseline comparability (8/14), unclear random sequence generation (5/14) and per-protocol analysis (5/14). The overall quality of evidence at outcome level ranged from moderate to very low because of risk of bias, insufficient sample size, small number of events, and wide 95% CI (eTables 1-16 in the Supplement).

Effects of interventions

Duration of systemic combination therapy ≤ 12 weeks

PASI 75

Nine trials[15,16,18-21,25,26,30] assessed the proportion of patients who attained a PASI 75. Two of these trials[16,18] found statistically significant differences in favor of etanercept plus methotrexate (MTX) with moderate quality of evidence (eTable 6 in the Supplement). Zachariae et al[18] found that 54.8% of patients in the etanercept plus MTX group attained PASI 75 compared with 25.0% in the etanercept plus MTX tapering group (MTX discontinued at week 4) (RR 2.19; 95% CI 1.07-4.49). Gottlieb et al[16] demonstrated that 77.4% of patients in the etanercept plus MTX group attained PASI 75 compared with 60.3% in the etanercept plus placebo group (RR 1.28; 95% CI

1.14-1.45). A trial by Wolf et al[26] found statistically significant differences in favor of ustekinumab plus UVB with very low quality of evidence. In patients treated with ustekinumab, 77.8% attained PASI 75 on UVB irradiated body halves compared with 11.1% on unirradiated body halves (RR 7.0; 95% CI 1.07-45.9) (eTable 5 in the Supplement).

PASI 90

Four trials[15,16,18,25] assessed the proportion of patients attaining PASI 90 or higher. The trial by Gottlieb et al[16] found a statistically significant difference, with 52.3% of patients in the etanercept plus MTX group attaining PASI 90 compared with 33.1% of patients in the etanercept plus placebo group (RR 1.58; 95% CI 1.27-1.97) (eTable 6 in the Supplement). Quality of evidence was moderate.

PGA of clear or almost clear

Five trials[15,16,18,20,25] assessed the proportion of patients who attained a PGA of clear or almost clear. Two trials[16,18] found a statistically significant difference between treatment groups with moderate quality of evidence in favor of etanercept plus MTX (eTable 6 in the Supplement). Gottlieb et al.[16] found that 72.0% in the etanercept plus MTX group attained a PGA of clear or almost clear compared with 54.4% in the etanercept plus placebo group (RR 1.32; 95% CI 1.15-1.52), and Zachariae et al.[18] found that 71.0% of patients in the etanercept plus MTX group attained a PGA of clear or almost clear compared with 39.3% in the etanercept plus MTX tapering group (RR 1.81; 95% CI 1.08-3.02).

Mean change in PASI

Nine trials[18,20,21,23-27,29] assessed the mean change in PASI from baseline. Three trials[26,27,29] demonstrated a statistically significant difference between treatment groups with very low quality of evidence. Wolf et al[26] found a mean change in PASI of 4.1 in favor of UVB irradiated body halves compared with UVB unirradiated body halves in patients treated with ustekinumab (eTable 5 in the Supplement), and Ezquerra et al[29] found a mean change in PASI of 4.6 in favor of acitretin plus calcitriol compared with acitretin monotherapy (eTable 13 in the Supplement). El-Mofty et al[27] found a mean change in PASI of 9.04 in favor of MTX monotherapy compared with sulfasalazine plus pentoxifylline (eTable 11 in the Supplement).

Mean and median time to clearance

Two trials[24,30] assessed the mean time to clearance. Danno et al[30] found a statistically significant difference of 2.5 weeks in favor of etretinate plus eicosapentaenoic acid (fish oil) compared with etretinate monotherapy (eTable 15 in the Supplement). Quality of evidence was very low.

Table 1 Characteristics of included studies

Study reference	Year	Study design	No. of patients	Baseline disease severity	Intervention
Phototherapy in combination with traditional systemic agents[a]					
Mahajan et al.[17]	2007	RCT, single-blinded, ITT analysis	N = 40	>10% of body surface involvement	UVB thrice weekly + MTX 0.5 mg/kg
Asawanonda et al.[14]	2006	RCT, double blind, ITT analysis	N = 24	>20% of body surface involvement	UVB thrice weekly + MTX 15mg/wk
Shehzad et al.[22]	2004	RCT, open-label per protocol analysis	N = 60	PASI > 10	PUVA 4 treatments/wk + MTX 10mg/wk
Prystowsky et al.[23]	1996	RCT, Patient-blinded, per-protocol analysis	N = 19	>20% of body surface involvement	UVB 4 treatments weekly + calcitriol 0.5-2.0 μg/day
Gupta et al.[24]	1989	RCT, Double-blind, Per-protocol analysis	N = 20	10 – 50% of body surface involvement	UVB twice/wk + 10 capsules eicosa-pentaenoic acid daily
Phototherapy in combination with biologics					
Lynde et al.[15]	2012	RCT, investigator-blinded, ITT-analysis	N = 75	PASI > 10	UVB thrice weekly + Etanercept 50mg/wk
Park et al.[25]	2012	RCT, Open-label, ITT-analysis	N = 30	PASI > 10 and >10% of body surface involvement	UVB thrice weekly + Etanercept 50mg/wk
Wolf et al.[26]	2011	RCT, left-right, open-label, per-protocol analysis	N = 10	PASI > 10	UVB thrice weekly + Ustekinumab 45 or 90mg at week 0 and 4

	Control group	Study length (wk)	Follow up (wk)	Efficacy outcome measures used in study analysis	Safety outcome measures used in study analysis	Other outcome measures used in study analysis
	Placebo + UVB thrice weekly	24	12	PASI 75 Withdrawal due to lack of efficacy	% patients with AEs	Mean time to clearance/ relapse
	Placebo + UVB thrice weekly	24	24	PASI 90 Mean change in PASI	% patients with AEs Withdrawal due to AEs	Median time to clearance/relapse Mean change in DLQI
	1. PUVA 4 treatments/wk 2. MTX 10mg/wk	32	-	Mean change in PASI	-	Mean time to clearance
	UVB 4 treatments weekly + placebo	5	-	Mean change in PASI (scale 0-16)	-	-
	UVB twice/wk +10 capsules olive oil daily	8	-	Mean change in PASI (scale 0-18)		-
	Etanercept 50mg/wk	12	-	PASI 75/ PASI 90 PGA of clear/ almost clear Withdrawal due to lack of efficacy	% patients with SAEs	Mean change in DLQI
	Etanercept 50mg/wk	12	-	PASI 75/ PASI 90 PGA clear or almost clear Mean change in PASI	-	-
	Ustekinumab 45 or 90mg once every three weeks	6	-	PASI 75 Mean change in PASI	% patients with AEs/ Withdrawal due to AEs	-

Table 1 Continued

Study reference	Year	Study design	No. of patients	Baseline disease severity	Intervention	
Biologics in combination with traditional systemic agents						
Gottlieb et al.[16]	2012	RCT, double-blind, ITT-analysis	N = 478	PASI > 10/ >10% of body surface involvement	Etanercept 50mg/wk + MTX 7.5-15.0 mg/wk	
Zachariae et al.[18]	2008	RCT, open-label, ITT-analysis	N = 60	PASI > 8/ >10% of body surface involvement	Etanercept 50mg twice weekly for 12 weeks then 50mg/wk + MTX > 7.5mg/wk	
Gisondi et al.[19]	2008	RCT, investigator-blinded, ITT-analysis	N = 60	Clinically stable moderate to severe plaque type psoriasis	Etanercept 50mg/wk + acitretin 0.4mg/kg/day	
Combination of traditional systemic agents						
Study reference	Year	Study design	No. of patients	Baseline disease severity	Intervention	
El-Mofty et al.[27,b]	2011	RCT, unclear blinding, ITT-analysis	N = 16	>25% of body surface involvement	Sulfasalazine 2g/day + pentoxifylline 1200mg/ day	
Mittal et al.[20]	2009	RCT, double-blind, ITT-analysis	N = 41	>20% of body surface involvement	Acitretin 25mg/day + pioglitazone hydrochloride 15mg/ day	
Gupta et al.[28,c]	2007	RCT, open-label, per-protocol analysis	N = 24	PASI > 10/ >10% of body surface involvement	MTX 15mg/wk + betamethasone 3mg/wk	
Ezquerra et al.[29]	2007	RCT, unblinded, per-protocol analysis	N = 40	PASI > 15 and < 40	Acitretin 25mg/d + calcitriol 0.25 μg/d	

	Control group	Study length (wk)	Follow up (wk)	Efficacy outcome measures used in study analysis	Safety outcome measures used in study analysis	Other outcome measures used in study analysis
	Etanercept 50mg/wk + Placebo	12	-	PASI 75/PASI 90 PGA clear or almost clear Withdrawal due to lack of efficacy	% patients with AEs and SAEs/ Withdrawal due to AEs	-
	Etanercept 50mg twice weekly for 12 weeks then 50mg/wk + MTX discontinued at wk4	24	-	PASI 75/PASI 90 PGA clear or almost clear Mean change in PASI Withdrawal due to lack of efficacy	% patients with AEs and SAEs/ Withdrawal due to AEs	Mean change in DLQI
	1. Etanercept 50mg/wk 2. Acitretin 0.4mg/kg/ day	24	-	PASI 75 Withdrawal due to lack of efficacy	% patients with AEs	-

	Control group	Study length (wk)	Follow up (wk)	Efficacy outcome measures used in study analysis	Safety outcome measures used in study analysis	Other outcome measures used in study analysis
	MTX 25mg/wk	8	-	Mean change in PASI Withdrawal due to lack of efficacy	% patients with AEs	-
	Acitretin 25mg/day + placebo	12	-	PASI 75 PGA clear or almost clear Mean change in PASI Withdrawal due to lack of efficacy	% patients with AEs and SAEs/ Withdrawal due to AEs	-
	MTX 15mg/wk	?	?	-	-	Mean time to clearance Mean time to relapse
	Acitretin 25mg/d	12	-	Mean change in PASI	% patients with AEs	-

Table 1 Continued

Study reference	Year	Study design	No. of patients	Baseline disease severity	Intervention	
Combination of traditional systemic agents						
Reitamo et al.[21,b]	2001	RCT, double-blind, ITT-analysis	N = 33	PASI > 12	Sirolimus 3.0mg/m/d + cyclosporine 1.25mg/kg/d	
Danno et al.[30]	1998	RCT, unblinded, ITT-analysis	N = 40	Moderately involved, chronic plaque type psoriasis	Etretinate 20mg/d+ eicosapentaenoic acid 1800mg/d	

[a] Concomitant treatment with phototherapy and acitretin was excluded, because for this type of combination therapy, an overview of RCT evidence according to the GRADE approach already exists.
[b] Only the most clinically relevant comparisons are reported (sulfasalazine plus pentoxifylline vs. MTX monotherapy and sirolimus 3.0 mg/m/d + cyclosporine 1.25 mg/kg/d vs. sirolimus 5 mg/kg/d))
[c] Efficacy in terms of PASI outcomes were based on non-randomized patients

Withdrawal because of lack of efficacy

Four trials[15,16,20,27] assessed the proportion of patients who were withdrawn because of lack of efficacy. No statistically significant differences among treatment groups could be found, and quality of evidence was very low.

Mean change in DLQI

A trial by Lynde et al[15] assessed the mean change in DLQI from baseline. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Duration of systemic combination therapy > 12 weeks

PASI 75

Three trials[17-19] assessed the proportion of patients who attained PASI 75. Two trials found a statistically significant difference between treatment groups.

Mahajan et al[17] found that 95% in the UVB plus MTX group attained PASI 75 compared with 70% in the UVB plus placebo group (RR 1.36; 95% CI 1.0-1.84), with very low quality of evidence (eTable 1 in the Supplement). Zachariae et al[18] found that 71.0% of patients in the etanercept plus MTX group attained PASI 75 compared with 35.7% in the etanercept plus MTX tapering group (RR 1.99; 95% CI 1.15-3.43) with moderate quality of evidence (eTable 6 in the Supplement).

	Control group	Study length (wk)	Follow up (wk)	Efficacy outcome measures used in study analysis	Safety outcome measures used in study analysis	Other outcome measures used in study analysis
	Cyclosporine 5mg/kg/d	8	4	PASI 75 Mean change in PASI	Withdrawal due to adverse events	-
	Etretinate 20mg/d	12	-	PASI 75 (scale 0 to 12)	% patients with AEs	Mean time to clearance

Abbreviations: AE, adverse effect; DLQI, Dermatology Life Quality Index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ITT, intention to treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PUVA, psoralen-UV-A; RCT, randomized clinical trial; SAE, severe adverse event

PASI 90

Two trials[14,18] assessed the proportion of patients who attained PASI 90. A trial by Asawanonda et al[14] found a statistically significant difference between treatment groups, with 90.9% of patients in the UVB plus MTX group attaining PASI 90 compared with 38.5% in the UVB plus placebo group (RR 2.36; 95% CI 1.16-4.82) (eTable 1 in the Supplement). Quality of evidence was very low.

PGA of clear or almost clear

A trial by Zachariae et al[18] assessed the proportion of patients who attained a PGA of clear or almost clear and had a statistically significant difference, with 67.7% of patients in the etanercept plus MTX group compared with 35.7% in the etanercept plus MTX tapering group attaining a PGA of clear or almost clear (RR 1.90; 95% CI 1.09-3.30) (eTable 6 in the Supplement). Quality of evidence was very low.

Mean change in PASI

Three trials[14,17,18] assessed the mean change in PASI from baseline. Two trials found a statistically significant difference with very low quality of evidence. Zachariae et al[18] found a mean change in PASI of 5.1 in favor of MTX plus etanercept compared with etanercept plus MTX tapering (eTable 6 in the Supplement), and Asawanonda et al[14] found a mean change in PASI of 7.75 in favor of UVB plus MTX compared with UVB plus placebo (eTable 1 in the Supplement).

Mean and median time to clearance

Four trials[14,17,22,28] assessed the mean or median time to clearance and found statistically significant differences between treatment groups, with very low quality of evidence. Gupta et al[28] found a difference in time to clearance of 9.3 days in favor of MTX plus bethametasone compared with MTX monotherapy (eTable 12 in the Supplement). Shehzad et al[22] found a difference in time to clearance in favor of Psoralen-UV-A (PUVA) plus MTX of 3 weeks compared with PUVA monotherapy and of 5.5 weeks compared with MTX monotherapy (eTables 2 and 3 in the Supplement). Asawanonda et al[14] found a time to clearance of 4 weeks for UVB plus MTX compared with >24 weeks for UVB plus placebo, and Mahajan et al[17] found a difference in mean time of clearance of 6 weeks in favor of UVB plus MTX compared with UVB plus placebo (eTable 1 in the Supplement).

Time to relapse

Three trials[14,17,28] assessed the mean or median time to relapse. Gupta et al[28] demonstrated a statistically significant difference of 53.24 days in favor of MTX plus bethametasone compared with MTX monotherapy with very low quality of evidence (eTable 12 in the Supplement).

Withdrawal because of lack of efficacy

Three trials[17-19] assessed the proportion of patients who were withdrawn because of lack of efficacy. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Mean change in DLQI

Two trials[14,18] assessed the mean change in DLQI from baseline. No statistically significant differences between treatment groups were found, and quality of evidence was very low.

Overall summary across studies

Phototherapy in combination with traditional systemic agents

Small statistically significant differences in favor of UVB plus MTX[14,17] and PUVA plus MTX[22] were found. For UVB plus fish oil[24] and UVB plus calcitriol[23], no significant superiority was found. No major differences in safety profiles between treatment groups were found, and no SAEs were reported. Quality of evidence was very low for all outcomes in this section.

Phototherapy in combination with biologics

Small statistically significant differences in favor of UVB plus ustekinumab were found.[26] For UVB plus etanercept, no significant superiority was found.[15,25] No major

differences in safety profiles between treatment groups were found. No SAEs were reported in the combination therapy groups compared with 3 SAEs in the monotherapy groups; all were considered to be unrelated to study treatment. Quality of evidence was very low for all outcomes in this section.

Biologics in combination with traditional systemic agents

Statistically significant differences in terms of efficacy in favor of etanercept plus MTX were found, with moderate quality of evidence.[16,18] However, this effect coincided with a statistically significant increase in AEs. In the etanercept plus MTX group, 74.9% of patients experienced AEs compared with 59.8% of patients in the etanercept plus placebo group (RR 1.25; 95% CI 1.10-1.42). For infectious AEs, a statistically significant higher incidence was found in the combination therapy group compared with the group treated with etanercept plus placebo (34.7% vs. 25.9%; RR 1.34; 95% CI 1.02-1.76)[16]. _

Most AEs were considered mild to moderate. Five SAEs were reported in the etanercept plus MTX groups compared with 8 SAEs in the control groups (etanercept plus placebo and etanercept plus MTX tapering).

Seven SAEs were considered to be related to study medication: 2 in the combination therapy groups (infection and vomiting) and 5 in the control groups (infections, pustular psoriasis, heart insufficiency, and atrial fibrillation). Quality of evidence for safety outcomes ranged from moderate (AEs) to very low (SAEs) (eTable 6 in the Supplement).

For etanercept plus acitretin compared with etanercept monotherapy, dose reductions without loss of efficacy were found with very low quality of evidence.[19] No major differences in safety profiles between these treatment groups were found, and no SAEs were reported.

Combination of traditional systemic agents

Small statistically significant differences in favor of acitretin plus calcitriol[29], etretinate plus eicosapentaenoic acid[30], and betamethasone plus MTX[28] were found. For acitretin plus pioglitazone hydrochloride[20] and sirolimus plus cyclosporine[21], no significant superiority was found, although dose reductions were possible for sirolimus plus cyclosporine. Equal efficacy for sirolimus plus low-dose cyclosporine (1.25mg/kg) compared with cyclosporine monotherapy (5.0mg/kg) was found.[21] Statistically significant lower efficacy was demonstrated for sulfasalazine plus pentoxifylline compared with MTX monotherapy.[27]

No major differences in safety profiles between treatment groups were found. One SAE was reported in the monotherapy groups[20] compared with no SAEs in the combination therapy groups. Quality of evidence was very low for all outcomes in this section.

Discussion

Several RCTs have been conducted in the field of combination therapy with systemic agents, but only one large-scale, methodologically well-designed clinical trial exists.[16] All combination therapies evaluated in this study had either superior or similar efficacy compared with control groups except for one study which showed lower efficacy for sulfasalazine plus pentoxifylline compared with MTX monotherapy[27]. The RCT conducted by Gottlieb et al[16] (moderate quality of evidence) contributes to the evidence of the superior efficacy of etanercept plus MTX over etanercept monotherapy in the short term, although this increased efficacy was accompanied by a higher incidence of AEs and, specifically, significantly more infectious AEs. The AEs were mild to moderate, and the incidence of SAEs was low and comparable in both treatment groups. For 6 other combination therapies with systemic agents, statistically significant superiority for some outcomes was found (very low quality of evidence mainly because of insufficient sample sizes). Some of these combination therapies could be valuable in high need patients, but more high-quality research is needed before recommendations for clinical practice can be made.

When comparing baseline characteristics of patients enrolled in RCTs of combination therapies[17-30] with baseline characteristics of patients enrolled in large-scale RCTs of single agents[31-37], no to minor differences in disease severity, disease duration, or prior systemic therapies were found for most comparisons. However, in 5 combination therapy trials (PUVA plus MTX[22], UVB plus fish oil[24], sulfasalazine plus pentoxifylline[27], acitretin plus calcitriol[29] and sirolimus plus cyclosporine[21]), patients with more severe and relatively more difficult-to-treat psoriasis were included compared with patients included in large-scale, systemic single-agent RCTs.[31-37]

Overall safety profiles for combination therapy with systemic agents seem tolerable in the short term, and the incidence of SAEs was very low. Long-term data are missing. Real-life data from observational registries may additionally inform us in the future and will be needed to monitor the long-term safety profile of combination therapy with systemic agents.

Potential biases and limitations in this study are as follows. There was significant heterogeneity in clinical outcome measures and treatment duration between trials included in this study, which may influence the precision of overall effect sizes and make it impossible to combine results in a meta-analysis. To obtain a complete overview on efficacy and safety of systemic combination therapy, it would be of interest to add data from high quality observational studies. Small controlled studies might not provide substantial greater evidence compared with open observational trials.

Conclusions

Implications for practice

The available clinical evidence on the efficacy and safety of combination therapy with systemic agents reveals that most evidence currently exists for the superior efficacy of etanercept plus MTX in the short term. This combination therapy may be beneficial in the treatment of therapy-resistant patients. However, treatment should be well-monitored, and dose reductions of either agent should be taken into consideration to minimize AEs. Unfortunately, all other combination therapies included had very low quality of evidence for all outcomes selected for this review. The lack of good data for these combination therapies does not mean that these combinations are not valuable, but only that they did not have enough power to provide evidence-based recommendations. In severe therapy-resistant patients, the introduction of these systemic combination therapies with well-monitored follow-up could be considered.

Implications for research

Long-term, methodologically well-designed studies with adequate sample size achieved by performing a priori power and sample size calculations that compare the different combination therapies with monotherapy and other combination therapies are needed. To improve the comparability of data, clinical homogeneity should be reached by clear descriptions of the populations (e.g., isolated plaque-type psoriasis or involvement of joints [arthritis psoriatica], disease severity, durations of treatment, outcome measurements, and time points of assessments). Future studies should include assessments of quality of life. Furthermore, future trials must be performed with sufficient duration to report the efficacy of the intervention (preferably $>$ 24 weeks), and follow-up must be long enough to be able to detect AEs and relapse rates after treatment discontinuation.

Supplemental material

The following supplemental material is available online: http://archderm.jamanetwork.com/article.aspx?articleid=1899249

- eTable 1 'Evidence profile UVB plus MTX vs. UVB monotherapy'
- eTable 2 'Evidence profile PUVA plus MTX vs. PUVA monotherapy'
- eTable 3 'Evidence profile PUVA plus MTX vs. MTX monotherapy'
- eTable 4 'Evidence profile etanercept plus UVB vs. etanercept monotherapy'
- eTable 5 'Evidence profile ustekinumab plus UVB vs. ustekinumab monotherapy'
- eTable 6 'Evidence profile etanercept plus MTX vs. etanercept monotherapy'
- eTable 7 'Evidence profile etanercept plus acitretin vs. etanercept monotherapy'
- eTable 8 'Evidence profile etanercept plus acitretin vs. acitretin monotherapy'
- eTable 9 'Evidence profile Acitretin + Pioglitazonehydrochloride vs. acitretin plus placebo'
- eTable 10 'Evidence profile sirolimus 3.0mg plus cyclosporine 1.25mg vs. cyclosporine 5mg monotherapy'
- eTable 11 'Evidence profile sulfasalazine plus pentoxifylline vs. MTX monotherapy'
- eTable 12 'Evidence profile MTX + oral betamethasone vs. MTX monotherapy'
- eTable 13 'Evidence profile acitretin plus calcitriol vs. acitretin monotherapy'
- eTable 14 'Evidence profile UVB plus Calcitriol vs. UVB plus Placebo'
- eTable 15 'Evidence profile etretinate plus eicosapentaenoic acid vs. etretinate monotherapy'
- eTable 16 'Evidence profile UVB plus fish oil vs. UVB monotherapy'
- eFigure 1: Search in MEDLINE

References

1. Jensen P, Skov L, Zachariae C. Systemic combination treatment for psoriasis: a review. Acta Derm Venereol. 2010;90(4):341-9
2. Gustafson CJ, Watkins C, Hix E et al. Combination therapy in psoriasis: an evidence-based review. Am J Clin Dermatol. 2013;14(1):9-25.
3. Bailey EE, Ference EH, Alikhan A, et al. Combination treatments for psoriasis: a systematic review and meta-analysis. Arch Dermatol. 2012;148(4):511-22.
4. http://guidance.nice.org.uk/. Accessed October 2012.
5. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. doi:10.1111/j.2010.1468
6. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
7. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137-74.
8. Nast A, Boehncke WH, Mrowietz U, et al. S3-guidelines on the treatment of psoriasis vulgaris. Update. J Dtsch Dermatol Ges. doi:10.1111/j.2012.1610.
9. Guyatt GH, Oxman AD, Vist G, et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J. 2008;336(7650):924-926.
10. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
11. Glanville JM, Lefebvre C, Miles JN, Camsosso-Stefinovic J. How to indentify randomized controlled trials in MEDLINE: ten years on. J Med Libr Assoc. 2006;94(2):130-6.
12. GRADEpro. http://ims.cochrane.org/gradepro. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008.
13. Guyatt GH, Oxman AP, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. J Clin Epidemiol. 2011;64(12):1283-1293.
14. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. J Am Acad Dermatol. 2006;54(6):1013–1018.
15. Lynde CW, Gupta AK, Guenther L, et al. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. J Dermatolog Treat. 2012;23(4):261-7.
16. Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2012;167(3):649-57.
17. Mahajan R, Kaur I, Kanwar AJ. Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis: a randomized single-blinded placebo-controlled study. J Eur Acad Dermatol Venereol. 2010;24(5): 595-600.
18. Zachariae C, Mork NJ, Reunala T, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88(5):495–501.
19. Gisondi P, Del Giglio M, Cotena C, et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol. 2008;158(6):1345–1349.
20. Mittal R, Malhotra S, Pandhi P, et al. Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. Arch Dermatol. 2009;145(4): 387–393.

21. Reitamo S, Spuls P, Sassolas B, et al. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. Br J Dermatol. 2001;145(3):438–445.
22. Shehzad T, Dar NR, Zakria M. Efficacy of concomitant use of PUVA and methotrexate in disease clearance time in plaque type psoriasis. J Pak Med Assoc. 2004;54(9):453–455.
23. Prystowsky JH, Knobler EH, Muzio PJ. Oral calcitriol (1,25-dihydroxyvitamin D3) does not augment UVB phototherapy for plaque psoriasis. J Am Acad Dermatol. 1996;35(2Pt1):272-4.
24. Gupta AK, Ellis CN, Tellner DC, et al. Double-blind, placebo-controlled study to evaluate the efficacy of fish oil and low-dose UVB in the treatment of psoriasis. Br J Dermatol. 1989;120(6):801-7.
25. Park KK, Wu JJ, Koo J. A randomized, 'head-to-head' pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients. J Eur Acad Dermatol Venereol. 2012;27(7):899-906.
26. Wolf, P., Weger, W., Legat, et al. Treatment with 311-nm ultraviolet B enhanced response of psoriatic lesions in ustekinumab-treated patients: a randomized intra-individual trial. Br J Dermatol. 2012;166(1):147–153.
27. El-Mofty M, el-Darouti M, Rasheed H et al. Sulfasalazine and pentoxifylline in psoriasis: a possible safe alternative. J Dermatolog Treat. 2011;22(1):31-7.
28. Gupta R, Gupta S. Methotrexate-betamethasone weekly oral pulse in psoriasis. J Dermatolog Treat. 2007;18(5):291–294.
29. Ezquerra GM, Regana MS, Millet PU. Combination of acitretin and oral calcitriol for treatment of plaque-type psoriasis. Acta Derm Venereol. 2007;87(5):449–450.
30. Danno K, Sugie N. Combination therapy with low-dose etretinate and eicosapentaenoic acid for psoriasis vulgaris. The Journal of Dermatology. 1998;25(11):703–705.
31. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139(12):1627-32.
32. Papp KA, Tyring S, Lahfa M, et al. Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152(6):1304-12.
33. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014-22.
34. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;14;349(7):658-65.
35. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. N Engl J Med. 2011;365(17):1586-96.
36. Kleinpenning MM, Smits T, Boezeman J, van de Kerkhof PC, Evers AW, Gerritsen MJ. Narrowband ultraviolet B therapy in psoriasis: randomized double-blind comparison of high-dose and low-dose irradiation regimens. Br J Dermatol. 2009;161(6):1351-6.
37. Kirke SM, Lowder S, Lloyd JJ, Diffey BL, Matthews JN, Farr PM. A randomized comparison of selective broadband UVB and narrowband UVB in the treatment of psoriasis. J Invest Dermatol. 2007;127(7):1641-6.

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Comparing treatment goals for psoriasis with treatment decisions in daily practice: results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE

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Abstract

Background: Treatment goals have been developed to optimize daily clinical practice psoriasis care, but have not yet been studied in real life.

Objectives: To investigate to what extent treatment decisions made by dermatologists in daily clinical practice for patients with psoriasis on biologics are already in accordance with treatment goals without the active application of the treatment goals algorithm.

Methods: Data were extracted from a prospective daily practice cohort of patients with psoriasis on biologics. Analysis was done on effectiveness (Psoriasis Area and Severity Index score) and quality of life (Dermatology Life Quality Index questionnaire). Treatment decisions such as dosage adjustments, combination treatments, or switching therapy were compared with the treatment goals algorithm.

Results: In 64% (253 of 395) of visits, physicians followed the treatment goals algorithm. There were 162 (41%) visits in which there should have been a treatment modification according to treatment goals (group Modify) and a modification was indeed made in 59 of these 162 visits (36%). In 233 (59%) visits no treatment modification was necessary (group Continue) and therapy was indeed not modified in 194 of 233 visits (83%).

Conclusions: Physicians acted in accordance with treatment goals in the majority of patient visits. In the patient group not achieving these goals, physicians should have modified therapy according to treatment goals but continued the same therapeutic regimen in the majority of visits. Optimizing therapy and defining barriers in the latter group might increase treatment results in daily practice psoriasis care.

Introduction

Psoriasis is a chronic skin disease with great impact on the quality of life (QoL) of patients.[1,2] Moderate-to-severe psoriasis is usually treated with systemic and biologic therapies, although undertreatment does occur.[3-5] In order to guide physicians with treatment decisions in daily practice, a European consensus on treatment goals was published in 2011.[3,6] These treatment goals advise to continue treatment when baseline Psoriasis Area and Severity Index (PASI) score has improved by at least 75% (PASI≥75; treatment success) or when a Dermatology Life Quality Index (DLQI) score of ≤ 5 is reached in patients with a PASI score improvement of between 50% and 75% (PASI50-75; intermediate response). In contrast, treatment should be adjusted when PASI50 is not reached (treatment failure) or when treatment response is intermediate with a DLQI score of >5.[3] Modification strategies include increasing dosage of current therapy or reducing treatment intervals, adding topical or systemic therapy, or changing the drug.[6] Treatment goals are shown in Figure 1. Recently, treatment goals have been evaluated for adalimumab therapy using data from three randomized clinical trials (CHAMPION, REVEAL and BELIEVE).[7] However, treatment goals have been formulated for use in daily clinical practice and it is known that the daily practice patient differs substantially from the clinical trial patient.[8] In addition, daily practice patients are being treated according to the opinion of their physician and therefore treatment decisions may vary considerably.

The main objective of this study was to investigate to what extent treatment decisions made in clinical practice are already in accordance with the treatment goals without the active application of the treatment goals algorithm. This may allow us to identify the gap between daily practice and the future situation after optimal implementation of treatment goals.

Methods

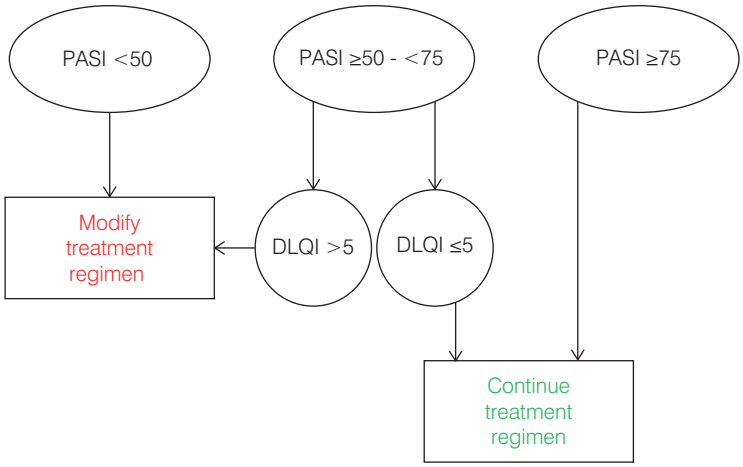
BioCAPTURE registry

For this study, data were used from the prospective registry BioCAPTURE that contains data from all patients with psoriasis treated with biologics from 2005 until now who gave informed consent. One academic and eight nonacademic centres participate in data collection. The BioCAPTURE registry was approved by the medical ethics committee of the Radboud University Medical Center.

Patients

Patients treated between 1 March 2010 and 31 December 2012 were included in the present analysis. Patient characteristics were collected including sex, family history of

Figure 1 Treatment goals in psoriasis. Adapted from Mrowietz, *et al*.[3]



psoriasis, psoriatic arthritis, mean baseline PASI score at the start of therapy, body mass index, age at onset of disease and age at start of the biologic. Patients were treated with biologics (etanercept, adalimumab, infliximab and ustekinumab) according to European and Dutch guidelines on psoriasis treatment. Patients were allowed to have multiple treatment episodes (TEs) that were defined as continuous treatment periods with one of the aforementioned biologics. A treatment interruption of 90 days during treatment with the same drug was allowed. During treatment, patient visits were scheduled every 3 months.

Assessments

To measure psoriasis severity, PASI scores were calculated at every visit and registered in the database.[9] Physicians were trained by an experienced research nurse to assess PASI scores. Scores were regularly double-checked by this nurse. From March 2010, DLQI measures were conducted every 3 months during the first year and every year thereafter in patients starting on biologics or switching to new biologics. The DLQI is a validated questionnaire measuring QoL in patients with dermatological conditions and has been translated into different languages.[10,11] Lower DLQI scores indicate better QoL. Data on biologic treatment, conventional systemic and intensive topical (i.e., dithranol) treatment during study period were recorded, as well as dosages of antipsoriatic medication. PASI scores, DLQI data and information on treatment decisions were extracted from the database for patient visits at baseline (i.e., start of medication) and at months 3, 6, 9 and 12. During patient

visits, PASI scores were visible for treating physicians whereas PASI percentages compared with baseline and DLQI scores were not. Therefore, patients were treated without the knowledge of whether patients reached treatment goals criteria for treatment modification or continuation of treatment without modification (Fig. 1).

Data analysis

PASI scores were compared with baseline (month 0) in order to calculate PASI percentages for included visits. Hereafter, patient visits were grouped into three PASI percentage groups according to treatment goals in order to calculate the number of visits with treatment success (i.e., PASI≥75): (1) PASI<50, (2) PASI50-75 and (3) PASI≥75. In accordance with the treatment goals, the DLQI was calculated for patient visits in the intermediate response group (PASI50-75) to discriminate between high QoL (DLQI ≤ 5) and low QoL (DLQI > 5). If no DLQI score was available for a visit in the intermediate group, this visit was excluded from further analyses. Subsequently, information on treatment decisions for all included visits were extracted from the database at months 3, 6, 9 and 12 with a range of 2 weeks prior to and 2 weeks after the defined month. After that, patient visits were grouped into (a) group Modify, in which treatment modification is being recommended according to treatment goals and (b) group Continue, in which the treatment regimen may be continued and no treatment modifications are necessary according to treatment goals. In these two groups, it was recorded how often modifications were indeed carried out, and how often treatment was not changed.

Treatment modifications made by physicians were described and grouped as follows: (1) increasing dose (or reducing dose intervals) of the biologic, (2) increasing dose of the conventional systemic drug, (3) increasing dose of both biologic and conventional systemic drug, (4) decreasing dose of biologic, (5) decreasing dose of conventional systemic drug, (6) decreasing dose of both biologic and conventional systemic drug, (7) adding conventional systemic therapy to a biologic, (8) adding intensive topical therapy (i.e., dithranol), (9) switching of therapy, and (10) other modifications.

As baseline PASI scores might influence the ability to reach PASI 75, the median baseline PASI scores were calculated in the groups Modify and Continue, and compared. To assess the difference in QoL between the groups Modify and Continue, median DLQI scores were calculated and compared. For the group Modify, a subanalysis of DLQI was performed for patient visits in which a modification in treatment was indeed made compared with those visits in which the same therapeutic regimen was continued.

Statistics

Descriptive statistics were used and expressed as percentages, means ± standard deviations (SD) or median (range). In the case of repeated measures within patients

only descriptive statistics were used. Mann-Whitney U-test was used to compare baseline PASI scores between groups Modify and Continue. P-value was set at 0.05. IBM SPSS Statistics 20 (IBM, Armonk, NY, U.S.A.) was used for analyses.

Results

Patients

A total of 161 patients were identified from our cohort with 192 TEs (Fig. 2). TEs with only one PASI score at baseline or without a baseline PASI score were excluded (n=28). This resulted in 164 TEs from 139 patients and 454 visits for which a PASI percentage could be calculated. Patient characteristics are shown in Table 1. Of the 164 TEs, in 72 (44%) TEs adalimumab therapy was prescribed, 54 (33%) TEs etanercept, in 33 (20%) TEs ustekinumab and in 5 (3%) TEs infliximab therapy was prescribed.

Table 1 Patient characteristics

Patient characteristics	N = 139
Male gender, n (%); N= 139	88 (63.3)
Positive family history of psoriasis, n (%); N= 133	85 (61.2)
Psoriatic arthritis, n (%); N= 123	44 (31.7)
BMI, median [range]; N= 101	28.0 [17.7-53.2]
Baseline PASI score, median [range]; N= 139	11.2 [2.0-42.1]
Age at onset of psoriasis (years), mean ± SD; N= 136	24.8 ± 13.0
Age at start of biologic therapy (years), mean ± SD; N= 139	47.4 ± 13.0

BMI: Body Mass Index; PASI: Psoriasis Area and Severity Index

Assessments

There was a PASI50 in 30% (134 of 454), a PASI50-75 in 30% (138 of 454) and a PASI≥75 response (treatment success) in 40% (182 of 454) of visits (Fig. 2). After excluding 59 visits due to missing DLQIs, 395 visits were left for analyses. In 41% percent of visits (162 of 395) treatment should have been modified (group Modify) and in 59% (233 of 395) therapy did not have to be modified (group Continue) according to treatment goals. The median baseline PASI score was significantly lower in the group Modify (10.5 [0.6-38.4]) than in the group Continue (12.2 [3.8-42.1], P= 0.004)).

DLQI scores for included visits were grouped based on PASI percentage achieved (Fig. 3). In the group PASI<50 and PASI50-75 with a DLQI score, 41% and 35% of visits, respectively, showed a DLQI score of > 5, representing low QoL according to treatment goals. However, when PASI≥75 was reached, 19% of visits showed a DLQI > 5. In visits with a PASI≥75, 50% of DLQI scores were 0, indicating optimal QoL compared with 7% in visits with a PASI<50.
Median DLQI at visits for those in the group Modify was compared with median DLQI of patients on visits in the group Continue. Scores were 6.00 [0-30] and 1.00 [0-16] respectively, indicating a higher QoL in the group Continue.
Within the group Modify, two subgroups were present: one with treatment modification and one without modification (Fig. 2). Median DLQI at visits was compared between these subgroups: 7.00 [0-16] versus 6.00 [0-30] for modified and not modified, respectively.

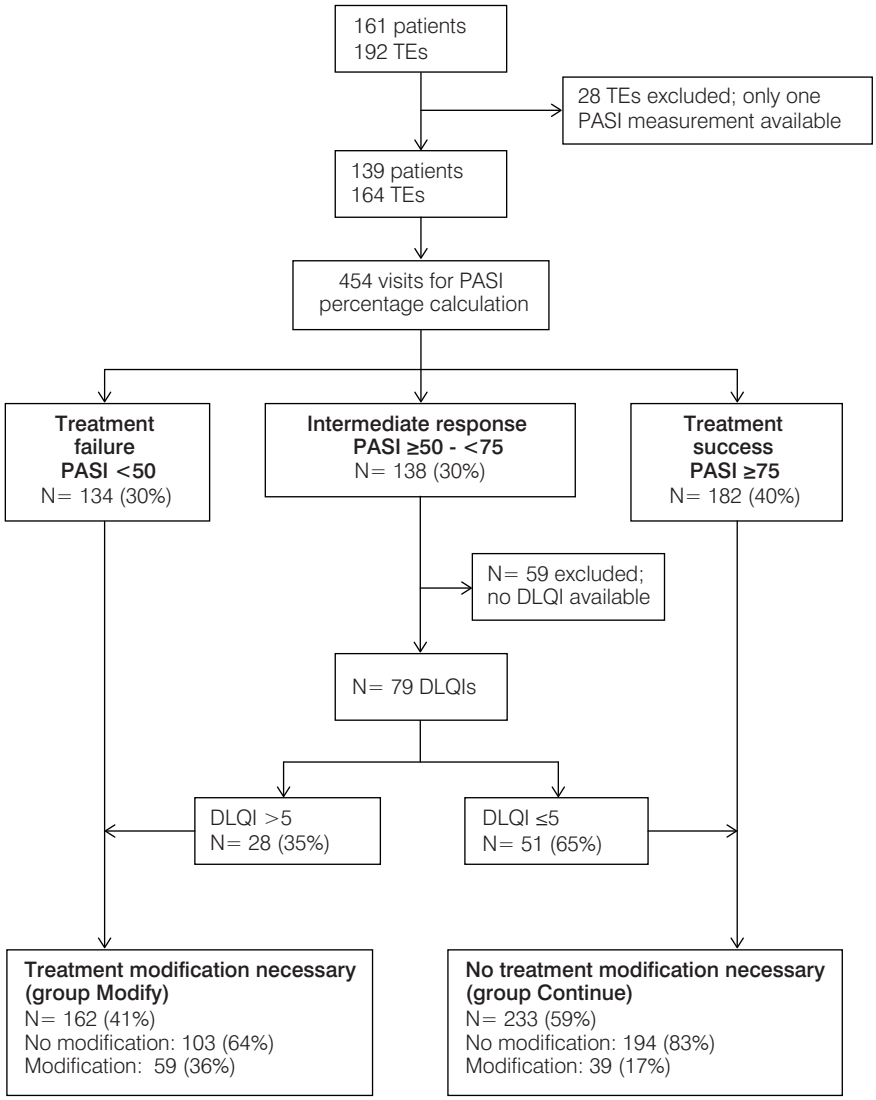
Treatment decisions

The treatment goals algorithm was followed by physicians in 64% (253 of 395) of visits (Fig. 2); in the group Modify, therapy was indeed modified in 59 of 162 visits, and in the group Continue therapy was continued without modification in 194 of 233 visits. Table 2 shows numbers of treatment decisions for the groups Modify and Continue. In both groups, there were no treatment modifications due to a serious adverse event.

Modification necessary according to treatment goals (group Modify)

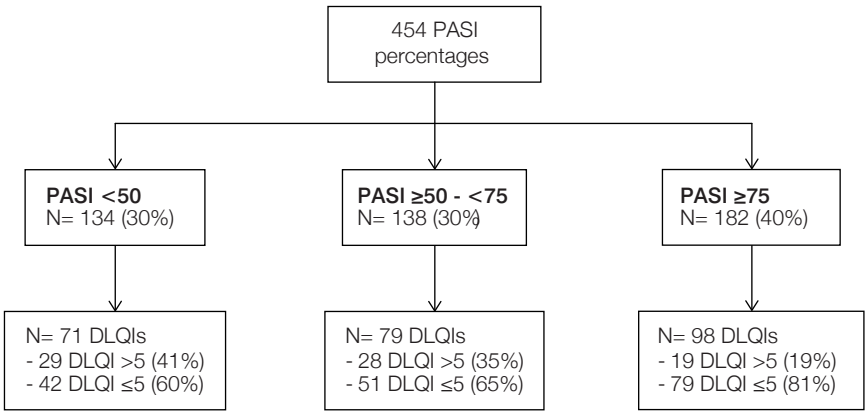
In the group Modify, in 36% (59 of 162) of visits therapy was indeed modified and in 64% (103 of 162) of visits therapy was not modified. There were 61 modifications (Table 2). Most often (46%; 28 of 61) a dose increase of biologic, conventional systemic or both was carried out. Of these, a dose increase of the biologic was the most frequently applied strategy. In 18% (11 of 61) of modifications there was a switch to another biologic. In 13% (8 of 61) of modifications there was an interruption or restart of biologic or conventional systemic therapy. In 11% of modifications (7 of 61) it was decided to decrease the dose of biologic or conventional systemic therapy, despite of a PASI<50 or a PASI50-75 with a DLQI>5. One dose decrease included etanercept from 2x50 mg per week to 1x50mg per week according to label at month 3. Conventional systemic therapy was stopped twice; methotrexate was stopped due to desire for pregnancy and cyclosporine was stopped because it was prescribed only as bridging therapy. By month 3, 41% (25 of 61) of modifications had already been made. At this time point, a switch to another biologic was the most frequently chosen treatment strategy, followed by a dose increase of biologic therapy.

Figure 2 Flow chart of PASI responses, DLQI scores and treatment modification in the prospective daily practice cohort BioCAPTURE



The treatment goals flow chart using daily practice data from patients with psoriasis on biologics in the BioCAPTURE cohort. TEs: treatment episodes; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality index

Figure 3 DLQI scores for different PASI percentage groups



DLQI scores from patients with psoriasis in the BioCapture cohort. DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index.

No modification necessary according to treatment goals (group Continue)

In the group Continue, in 83% (194 of 233) of visits the same therapeutic regimen was indeed continued. In 30 of 194 (15%) visits, the biologic dose could have been decreased by physicians because treatment goals were reached but a high dose was continued.

In 17% (39 of 233) of visits there were 40 modifications (Table 2). Most often (65%; 26 of 40) dose of biologic or conventional systemic was decreased. Of these, dose decrease of biologic was the most frequent. Twelve modifications included the decrease of etanercept dose from 2x50mg per week to 1x50 or 2x25mg per week according to label at month 3. In two modifications (5%), low-dose methotrexate was added as combination therapy. The dose of biologic was increased in 18% of modifications (7 of 40). As shown in Table 2, there was no switch of therapy in the group Continue. Forty-three percent of modifications (17 of 40) were made in month 3. The most frequently applied modification in this subgroup was a dose decrease of the biologic.

Table 2 Treatment modifications during patient visits in the daily practice cohort Biocapture

Treatment groups	Group Modify PASI < 50 and PASI ≥50-<75 + DLQI >5 N=162 (41%)	Group Continue PASI ≥50-<75 + DLQI ≤5 and PASI ≥75 N = 233 (59%)
No modification	103 (64%) visits	194 (83%) visits
Modification	59 (36%) visits; 61 modifications	39 (17%) visits; 40 modifications
1. Dose increase of		
- biologic	24	7
- conventional systemic	3	0
- both	1	0
2. Dose decrease of		
- biologic	3 (1 according to label)	20 (12 according to label)
- conventional systemic	4	6[a]
- both	0	0
3. Stop of		
- biologic	0	1[b]
- conventional systemic	2[b,c]	1[d]
4. Addition of		
-conventional systemic	3	2
- intensive topical therapy	1[e]	0
- both	0	0
5. Switching therapy to		
- biologic therapy	11	0
- conventional systemic	1	0
- intensive topical therapy	0	0
6. Other	8[f]	3[f]

Data are stated as N (%).

[a] One patient also restarted biologic therapy after an upper respiratory tract infection

[b] Due to desire for pregnancy

[c] One patient had a dose decrease of biologic and stopped conventional systemic therapy

[d] Due to adverse effects (somnolence)

[e] This patient also had a treatment interruption of biologic therapy due to liver function abnormalities

[f] Interruption or restart of biologic or systemic combination therapy due to, e.g., flu, urinary tract infection, other infections, liver function abnormalities

Discussion

In this prospective daily practice cohort of patients with psoriasis treated with biologics, in the majority (64%) of visits physicians followed the treatment goals algorithm intuitively. In 59% of visits, treatment goals were reached. In a large percentage of visits (64%) in which patients needed adjustment of therapy according to the treatment goals, no treatment modifications were made by physicians.

One study recently assessed adalimumab efficacy in three phase III clinical trials using the psoriasis treatment goals as evaluation method.[7] This study showed that in the CHAMPION, REVEAL and BELIEVE study at week 16, treatment success was achieved by 79.3%, 72.1% and 68.2% respectively. Moreover, treatment goals for continuing therapy without modification were reached by > 70% of patients. In our study, percentages were lower: 40% of visits achieving treatment success and 59% of visits reaching treatment goals. However, in the present analysis we used data from all biologics available instead of only adalimumab, and in a daily practice setting in contrast to a randomized controlled trial. In real life, treatments are known to show lower success rates.[12-14] To the best of our knowledge, this is the first daily practice study analysing to what extent advice resulting from following the treatment goal algorithm is followed in daily practice.

In the present study, physicians were unaware of the components of treatment goals (DLQI and PASI percentage) and therefore unaware of treatment failure or treatment success according to these goals. Although physicians were not using treatment goals, in the majority of visits physicians followed treatment goals algorithm intuitively. This can be explained by the high effectiveness of biologics in most visits, so physicians did not have to make changes to treatment strategies according to treatment goals. If patients did not reach treatment goals, it was shown that, in the majority of visits, physicians preferred to continue treatment without modification, so that is where there might be 'room for improvement'.

Achieving treatment success seems important for patients with psoriasis in order to reach a sufficient QoL. Using data from randomized clinical trials, Mattei *et al.*[15] have recently showed that patients treated with biological therapies have better QoL scores in the PASI≥75 group. The same results were seen in the daily practice situation in the present study. Patients with a PASI≥75 had better QoL scores more frequently, compared with patients in the remaining groups. Nineteen per cent of visits with a DLQI score showed low QoL (DLQI>5) in the PASI≥75 group compared with about 35-40% in the other two groups. Fifty per cent of DLQI scores were 0 in the PASI≥75 group, indicating optimal QoL, compared with only 7% in the PASI<50 group. These results strengthen the definition of treatment success in the treatment goals, i.e. achieving a PASI≥75 response compared with baseline. It must be noted that 19% of available DLQI scores in the group achieving PASI ≥75

indicated low QoL. It might be of interest to establish what needs are not fulfilled for these patients.

We analysed whether baseline PASI scores influenced the possibility for patients to achieve treatment goals. Patients with high baseline PASI scores might achieve treatment success, and therefore treatment goals, more easily compared with patients with low baseline PASI scores, as these are expressed with a relative measure. This is especially important in the comparison between patients naive or nonnaive (switchers) for biologics, as the latter group often starts with a lower baseline PASI. Median baseline PASI score at start was compared between the groups Modify and Continue and was significantly lower for the group Modify ($p=0.004$), although scores only differed with 1.7. This difference is small and will probably not explain why patients end up in the group Modify or Continue. In the current treatment goals there is no differentiation between naive and nonnaive patients.

Our cohort showed that in the group Modify, median DLQI was similar between patient visits with a treatment modification compared with visits without a treatment modification. Hence, in daily practice in which treatment goals were not being implemented, the decision to modify therapy seems not to be influenced by the patient's perceived QoL. It might therefore be worthwhile to conduct DLQI questionnaires prior to the clinical visit in order to identify those patients with a low QoL to optimize their care.

As shown, there is considerable 'room for improvement' in the care of patients with psoriasis. Optimized treatment might be achieved by the consequent application of treatment goals. In this respect, lessons can be learned from previous studies in rheumatoid arthritis, hypertension, and diabetes.[16-19] The TICORA study for tight control in rheumatoid arthritis showed that a strategy of intensive outpatient management compared with routine daily practice improved disease activity and QoL at no additional costs. However, mixed results are seen in diabetes care.[20] Furthermore, implementation research in the field of rheumatology has shown that there are many reasons not to modify treatment while treatment goals advised to do so.[21] These findings may also apply to the field of dermatology. Possible factors include the presence of comorbidities, comedication, safety issues, number of available treatments left, not being aware of PASI percentages and DLQI scores, and reticence in physicians and patients.

The current treatment goals flowchart does not incorporate dose decreases in patients who meet criteria for continued treatment without modification. Evidence for dose decrease of biologics beyond the label is scarce in the field of psoriasis. It should be worthwhile to focus on this issue in future studies in order to decrease costs and improve safety.

Other barriers to implementing treatment goals might include the requirement that physicians should assess PASI scores and conduct DLQI measurements during

patient visits. This requires optimal logistics and a time effort from physicians. Therefore it seems important to analyse further the impact of implementation of treatment goals on the care of patients with psoriasis.

A limitation of the present study is that topical treatments in combination with biologics were used as well, but not analysed in this study because data on nonintensive topicals were not completely recorded in the database. Another limitation is that there were missing data from DLQI questionnaires, which could lead to responder bias. However, the percentage of missing data was similar between groups. The strengths of this study are the inclusion of different clinical centers and doctors (both academic and nonacademic), the daily practice environment itself, and the 'blindedness' of doctors for DLQI scores and PASI percentages.

This study addresses European treatment goals in daily clinical practice. Results show that in daily practice in which treatment goals were not yet implemented, physicians usually followed treatment goals intuitively in visits in which treatment goals were achieved. On the other hand, in patients with suboptimal response to therapy, frequently the same therapeutic regimen was continued. This shows an urgent need for identification of barriers to using treatment goals and the need for implementation studies as this might increase the rate of treatment success and the number of patients with psoriasis with optimal QoL on systemic therapies including biologics in daily clinical practice.

References

1 Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009 Jul 30;361(5):496-509.

2 Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. PLoS One. 2012;7(12):e52935.

3 Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, Franke J, Antoniou C, Arenberger P, Balieva F, Bylaite M, Correia O, Daudén E, Gisondi P, Iversen L, Kemény L, Lahfa M, Nijsten T, Rantanen T, Reich A, Rosenbach T, Segaert S, Smith C, Talme T, Volc-Platzer B, Yawalkar N. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011 Jan;303(1):1-10.

4 Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol. 2013 Oct;149(10): 1180-5.

5 Nast A, Mrowietz U, Kragballe K, de Jong EM, Puig L, Reich K, Warren RB, Werner R, Kopkow C, Schmitt J. Barriers to the prescription of systemic therapies for moderate-to-severe psoriasis--a multinational cross-sectional study. Arch Dermatol Res. 2013 Dec;305(10):899-907.

6 Mrowietz U, Kragballe K, Nast A, Reich K. Strategies for improving the quality of care in psoriasis with the use of treatment goals--a report on an implementation meeting. J Eur Acad Dermatol Venereol. 2011 May;25 Suppl 3:1-13.

7 Mrowietz U, Kragballe K, Reich K, Griffiths CE, Gu Y, Wang Y, Rozzo SJ. An assessment of adalimumab efficacy in three Phase III clinical trials using the European Consensus Programme criteria for psoriasis treatment goals. Br J Dermatol. 2013 Feb;168(2):374-80.

8 Garcia-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Daudén E, Sánchez-Carazo JL, Alsina M, Herrera-Ceballos E, Gómez-García FJ, Ferrán M, López-Estebaranz JL, Hernanz JM, Belinchón-Romero I, Vilar-Alejo J, Rivera R, Carrascosa JM, Carazo C. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol. 2012 Apr;148(4):463-70.

9 Fredriksson T, Pettersson U. Severe psoriasis - oral therapy with a new retinoid. Dermatologica 1978;157:238-44.

10 Finlay AY, Basra MK, Piguet V, Salek MS. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. J Invest Dermatol. 2012 Oct;132(10):2464-5.

11 Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008 Nov;159(5):997-1035.

12 Van Lümig PP, Driessen RJ, Boezeman JB, Van De Kerkhof PC, De Jong EM. Long-term efficacy of etanercept for psoriasis in daily practice. Br J Dermatol. 2012 Feb;166(2):445-7.

13 Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66:1473–1478.

14 Shear NH, Hartmann M, Toledo-Bahena M. Long-term Efficacy and Safety of Infliximab Maintenance Therapy in Patients with Plaque-Type Psoriasis in Real-World Practice. Br J Dermatol. 2014 Mar 26. Doi 10.1111/bjd. 13004 [Epub ahead of print]

15 Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol. 2013 Feb 21. doi: 10.1111/jdv.12106. [Epub ahead of print]

16 Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004 Jul 17-23;364(9430):263-9.

17 Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. Diabetes Care. 2013 Aug;36(8):2271-9.

18 McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, Palazzini M, Park MH, Tapson VF, Sitbon O. Treatment goals of pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D73-81.

19 Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362: 1575-85.

20 Cooper-Dehoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010; 304: 61-8.

21 Van Hulst LT, Kievit W, van Bommel R et al. Rheumatoid arthritis patients and rheumatologists approach the decision to escalate care differently: results of a maximum difference scaling experiment. Artritis Care Res (Hoboken). 2011 Oct;63 (10): 1407-14.

PART V

SUMMARY AND DISCUSSION

13

Summary and discussion

Summary and discussion

In the Netherlands, approximately 500.000 persons suffer from psoriasis, of which ± ⅓ has moderate-severe to severe psoriasis. As stated in the introduction of this thesis, psoriasis is a skin disease with a major impact on the quality of life. Improving health care and optimizing treatment for patients with psoriasis is a continuous process in which scientific research is essential.

The goals of this thesis were to explore, compare and predict the effectiveness of biologics for psoriasis in daily practice with different measures for effectiveness (i.e., absolute and relative PASI scores), to explore drug survival (a composite measure for treatment success, i.e. effectiveness, safety, and patients' and physicians' behaviour) and to explore treatment success by combining drug survival with a skin-specific quality-of-life-questionnaire (i.e., the Dermatology Life Quality Index [DLQI]), to compare and predict long-term drug survival, as well as to explore the areas with room for improvement in daily practice psoriasis care. These studies are important for choosing the right therapy for the right patient and to improve the care of patients with psoriasis.

The studies included in this thesis are based on data from the literature and from BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics). BioCAPTURE is a prospective, multicenter cohort of patients with moderate to severe psoriasis, treated with biologics. Data on effectiveness, safety, patient reported outcome measures and cost-effectiveness are being collected. BioCAPTURE is established at the Department of Dermatology in the Radboudumc Nijmegen since 2005. From 2010, large regional centers have participated and at the moment, nine regional centers contribute to the BioCAPTURE registry. BioCAPTURE therefore represents data from both academic and non-academic centers.

Data from daily practice cohorts are important and relevant, because the real-world patient with psoriasis that is being treated in daily practice differs from the patients in RCTs.[1] Randomized controlled trials are essential in the development of new drugs, but have to be complemented with practice based evidence. Randomized controlled trials have a high internal validity but often a low external validity, whereas daily practice studies are intended to have a high external validity but often at the price of a low internal validity. Other differences between daily practice studies and RCTs are: (1) daily practice studies may include large numbers of patients and patients with different patient characteristics (i.e., higher age, more comorbidities, use of concomitant medication)[1], (2) daily practice studies may comprise a long period of follow-up[2], (3) treatment strategies in daily practice studies are different from RCTs (combination treatment, dose adjustments)[3], (4) daily practice studies are important when evaluating drug safety[4] as large numbers of patients with a longer period of follow-up can be evaluated, and (5) in daily practice studies, the behaviour of physicians and patients can be assessed[5].

In this chapter, the research questions from **Chapter 4** are answered and the results from studies described in **Chapter 5 – 12** are integrated and discussed. In addition, possibilities for future research are formulated.

Effectiveness

To explore

Research question 1: What is known thus far from literature on the effectiveness of biologics in daily practice psoriasis treatment?

The systematic review described in **Chapter 5** was performed to aggregate the available evidence on the effectiveness of biologics and conventional systemic agents in daily practice psoriasis treatment. Until then, no systematic review of effectiveness data of biologics and conventional systemic agents for psoriasis was available in the literature. The primary objective was to show the proportion of patients that reached PASI75 (a 75% reduction in baseline PASI score) with biologic treatments and/or conventional systemic agents at week 12-16 (short-term) in daily clinical practice. Other time points for evaluation of effectiveness were weeks 17-28 (intermediate-term) and ≥1 year (long-term).

Eventually, 32 studies were included. We showed that biologics and conventional systemic agents were effective in the treatment of psoriasis in daily practice. A substantial proportion of patients with psoriasis were achieving PASI75 with short-, intermediate- and long-term treatment, except for acitretin monotherapy.

The results of the effectiveness of biologics and conventional systemic agents in daily practice as showed in our systematic review are visualized in Table 1.

Ranges of PASI75 were large, especially for etanercept and adalimumab (Table 1).

In this systematic review, we encountered differences in study design (prospective / retrospective), differences regarding treatment regimens (e.g., dose adjustments, combination with conventional systemic agents), and patient characteristics (e.g. baseline PASI score, naïve/non-naïve).

A high heterogeneity in reporting cohort data from daily practice was encountered. Studies did not always specify important baseline characteristics such as baseline PASI score, or naivity to biologics. The use of concomitant antipsoriatic medication and the dose of biologics (dose increase, interval decrease or increase) was not mentioned in all studies. Hence, we made recommendations to improve the quality of reporting of daily practice studies.

Since the effect of dose adjustments and combination therapy with a conventional systemic agent was often not described in studies, it is possible that these treatment adjustments resulted in the large PASI75 ranges. In most studies on biologic therapies, concomitant conventional systemic agents were allowed and prescribed

Table 1 Effectiveness of biologics and conventional systemic agents from daily clinical practice. Data are based on the systematic review described in Chapter 5 of this thesis

Agent	PASI75 at week 12-16 daily practice
Ustekinumab	63% - 80%
Infliximab	38% - 53%
Adalimumab	27% - 68%
Etanercept	12% - 66%
Methotrexate	40% - 49%
Fumarates	47%
Cyclosporine	46%
Acitretin	27%

The reader is referred to the systematic review in Chapter 5 for the doses of the drugs.

by physicians. Mostly methotrexate was used for combination therapy. Another explanation was the use of dose adjustments. Especially in studies on adalimumab and etanercept, dose adjustments were allowed and prescribed by physicians.
Although results from RCTs and daily practice cannot be directly compared, PASI75 ranges achieved with antipsoriatic treatments in daily practice were in line with ranges stated in guidelines on psoriasis treatment.[6-8] We did not expect this, since earlier studies from our BioCAPTURE cohort and from other cohorts showed lower PASI75 percentages in daily practice than in RCTs.[9-11] Possible explanations for the similarity of achieved PASI75 percentages in daily practice and RCTs are the prescribed combination therapies and adjusted doses of biologics in daily clinical practice.
Evidence gaps identified by this systematic review were daily practice data on the effectiveness of infliximab, ustekinumab, conventional systemic agents, combination therapy of biologics with conventional systemic agents, long-term treatment and direct comparisons of effectiveness between anti-psoriatic agents.
With our systematic review we found only a small number of comparative studies in which biologics were compared with each other or were compared with conventional systemic agents. Most comparative studies were hampered by differences at start of treatment (e.g., baseline PASI score) which was not corrected for. Hence, a sound conclusion on the differences of effectiveness between biologics in daily practice was not possible. Therefore, we performed an analysis in which biologics for psoriasis were compared while correcting for confounders.

To compare

Research question 2: Which biologic has the highest confounder-corrected effectiveness in daily practice psoriasis treatment using data from the prospective BioCAPTURE cohort?

In **Chapter 6** we described the first prospective daily practice study with the objective to compare the effectiveness with PASI scores between the three widely used outpatient biologics adalimumab, etanercept and ustekinumab for patients with psoriasis, corrected for confounders. We took into account (1) the biologic dose, (2) combination treatment with a conventional systemic agent and (3) differences in baseline patient characteristics between the biologics, such as differences in PASI score at start of treatment. The primary objective was to compare the mean PASI descrease of adalimumab, etanercept and ustekinumab during the first 5 years of treatment. Secondary objectives were to compare the mean PASI decrease between these biologics during the first year of treatment, and the PASI75 at one year of treatment. Data from the multicenter BioCAPTURE cohort were used.

Results for the primary objective showed that patients treated with ustekinumab had a larger confounder-corrected mean PASI decrease compared with patients treated with etanercept during five years of treatment, without subanalyses for biologic dose. Secondary objective results showed that there were no differences in the confounder-corrected mean PASI decrease between biologics during the first year of treatment. On the other hand, patients treated with ustekinumab and adalimumab had a higher chance of achieving PASI75 compared with etanercept at one year of treatment, after correction for confounders.

We encountered differences in the use of biologic dose, especially regarding higher than label dose, between the outpatient biologics and found an influence of biologic dose on effectiveness results. Etanercept was most often prescribed in higher than label dose, followed by adalimumab and then ustekinumab. This might indicate that for dermatologists it was more difficult to achieve a good control of the psoriasis with normal doses of etanercept, than with normal doses of ustekinumab. This is confirmed by the observation that patients with a low-normal adalimumab, etanercept or ustekinumab dose (i.e., low to normal dose compared with expected label dose) during their treatment episode had a larger mean PASI decrease than the patients with a higher than label dose on the same biologic.

When the low-normal dosed treatment episodes were considered, no differences were found in confounder-corrected mean PASI decrease between biologics during one and 5 years of treatment. For the high-dosed treatment episodes, there were also no differences in confounder-corrected mean PASI decrease during one and 5 years. Considering PASI75, low-normal doses of adalimumab or ustekinumab were more effective than low-normal doses of etanercept at one year of treatment. Because ustekinumab (1) being significantly more often prescribed in a low-normal dose

compared with etanercept and (2) the low-normal dosed treatment episodes having a better mean PASI decrease compared with the high-dosed treatment episodes, ustekinumab showed on average better results than etanercept.

Also Strober *et al.* conducted a comparative daily practice study, but did not use PASI score nor accounted for the prescribed biologic doses.[12] Biologics were compared and effectiveness was evaluated using Physician Global Assessment (PGA of 0 or 1; respectively, "clear" or "minimal psoriasis"). This study showed that ustekinumab was superior to the anti-TNF agents adalimumab, etanercept and infliximab at month 6 and month 12.[12] In a meta-analysis using RCT data, ustekinumab was the most efficacious therapeutic alternative for moderate-to-severe psoriasis, followed by infliximab, adalimumab and etanercept.[13] In another recent meta-anaylis on RCT data, both adalimumab and ustekinumab had significantly higher PASI75 responses than etanercept.[14]

Differences in effectiveness results between biologics might be explained by the differences in mode of action between the biologics, with ustekinumab, by blocking IL-12 and IL-23, exerting its action more downstream in the cascade of cytokines than the anti-TNF-α agents adalimumab, etanercept and infliximab.[15] In addition, IL-23 seems to be an important cytokine in the immunopathogenesis of psoriasis, as evidenced by the high efficacy of newer biologics that only target this cytokine (anti-IL-23 biologic agents).[16] The difference in effectiveness between adalimumab and etanercept might be explained by the mode of action of adalimumab compared with etanercept. Etanercept is a TNF-α receptor antagonist, while adalimumab is a TNF-α antibody.[17,18] Another reason for differences in effectiveness might be the existence of non-measured confounders. Although we corrected for confounders, a comparison using real-world data raises more analytic difficulties than RCTs. However, one of the strengths of our study is high external validity as it comprises patients with comorbidities and comedication, and patients of higher age. As described previously, our results were in line with data from recent meta-analyses that used RCT data.Differences in effectiveness might also be explained by different genetic or cytokine profiles between patients with psoriasis.[19,20] The search for biomarkers as predictors for effectiveness gets currently much attention and could eventually lead to more targeted treatment.

To date, little is known on the effect of dose increase of biologics in the treatment of patients with psoriasis in daily clinical practice, although dose increase or interval reduction is used in daily practice.[21,22] At the moment, we do not know for which patient with psoriasis a dose increase is effective and we cannot predetermine this yet. Thus, more research is needed in order to advise dermatologists on the added value of dose increase of biologics compared with switching of the biologic and the cost-effectiveness of switching compared with short-term as well as long-term dose increase.

To predict

Research question 3: What are the predictors for high clinical effectiveness of biologics for psoriasis in daily clinical practice using data from BioCAPTURE?

In **Chapter 7** we focused on patients with psoriasis that reached a very high response, defined as PASI90, PASI100 or PASI≤5, at week 24 of biologic treatment. The objectives of our analysis with prospective daily practice data were to assess (1) the percentage of patients reaching high clinical response and (2) the predictors for achieving a high clinical effectiveness. Until then, no studies had assessed which patients with psoriasis were more likely to achieve these high clinical responses with biologic treatment.

We showed that PASI90 or PASI100 were rarely attained in daily practice psoriasis treatment with biologics (adalimumab, etanercept, infliximab and ustekinumab analyzed as one group). In 15% of treatment episodes PASI90 was reached and in only 3% of treatment episodes PASI100 was reached at week 24. Psoriasis Area and Severity Index≤5 (59% of treatment episodes) and even PASI≤2 (24% of treatment episodes) were more often achieved than PASI90 at week 24. This shows the importance of including an absolute PASI score in the assessment of psoriasis severity.

The use of a relative PASI score can therefore lead to 'false-negatives', i.e. patients that do have a high clinical response according to the absolute PASI score, but which is not reflected by the relative PASI score. This can be explained by the dependence of the relative PASI score on the baseline PASI score. It is more easy to achieve a PASI90 in patients with a high baseline PASI score compared with patients with low PASI scores at start of treatment. We showed this in our study after analyzing predictors for achieving a high clinical response at week 24 of biologic treatment. Patients with a baseline PASI≥10 had a higher chance of achieving PASI90 at week 24 than patients with a baseline PASI<10. Patients with a baseline PASI<10 had a higher chance of reaching PASI≤5 at week 24 than patients with a baseline PASI≥10. An additional predictor for achieving PASI≤5 at week 24 of biologic treatment was a lower baseline BMI in our study. Thus, patients with a lower baseline BMI had a higher chance of reaching an absolute PASI≤5 at week 24. Baseline BMI and baseline PASI score did not correlate with each other, and therefore baseline BMI was an independent predictor.

In our study we performed sensitivity analyses for (1) adalimumab/etanercept as one group (excluding infliximab and ustekinumab), (2) treatment episodes with a low to normal biologic dose, (3) treatment episodes without a treatment interruption, (4) treatment episodes without combination therapy, (5) weight instead of BMI, and (6) PASI≤3 because all treatment episodes with a PASI90 at week 24 also achieved PASI≤3 at week 24. These performed sensitivity analyses showed the robustness of our results with PASI≥10 being a predictor for PASI90, and PASI<10 as well as a lower BMI (or weight) being predictors for PASI≤5 (or PASI≤3).

The finding that weight and weight loss of patients with psoriasis have an influence on the efficacy of antipsoriatic treatment, is suggested in literature, but high quality RCTs are missing.[23-28] However, not every study that was conducted in patients with psoriasis found an influence of obesity on the effectiveness of biologics.[29] Additional studies are needed in order to answer the question whether weight loss is a good option to improve control of psoriasis in overweight or obese patients or that we should work towards creating BMI-based dosing of biologics.

Noteworthy, obesity also seems to play a negative role in the response to biologic treatment of other immune-mediated diseases, such as rheumatoid arthritis[30,31], ankylosing spondylitis and non-radiographic axial spondyloarthritis[32], psoriatic arthritis[33] and Crohn's disease[34].

Possible explanations that obesity can influence the effect of biologics are the modification of the drug distribution, as well as the increase of certain pro-inflammatory cytokines produced by the adipose tissue so that treatment is less efficacious with the same biologic dose in obese patients than in non-obese patients.[35]

Conclusions for effectiveness

- Biologics and conventional systemic agents are effective in the treatment of psoriasis in daily practice.
- Ustekinumab is, compared with etanercept, significantly more effective in decreasing the PASI score during the first 5 years of psoriasis treatment in daily practice.
- Ustekinumab is, compared with adalimumab and etanercept, the biologic that is most often prescribed in low to normal dose during a treatment period of 5 years in our cohort.
- It is important to include an absolute PASI score in the assessment of psoriasis severity, because the relative PASI score might not reflect a high clinical response in patients with PASI<10 at start of treatment.
- Patients with a baseline PASI≥10 have a higher chance of achieving PASI90 at week 24 than patients with a baseline PASI<10. Patients with a baseline PASI<10 have a higher chance of reaching PASI≤5 at week 24 than patients with a baseline PASI≥10.
- Baseline BMI is an important, modifiable predictor for reaching a high clinical response (PASI≤5, but also PASI≤3) with biologics in daily practice psoriasis treatment at week 24.

Drug survival

Drug survival of biologic treatment is the probability that a patient is still treated with a biologic after a period of time. Drug survival can be assessed for different reasons of discontinuation. Reasons for discontinuation are ineffectiveness, side-effects, pregnancy wish, and other reasons such as patient wish. In overall drug survival, all reasons of treatment discontinuation are included (i.e., discontinuation in general). Drug survival can also be split for discontinuation due to ineffectiveness or discontinuation due to side-effects.
We performed two drug survival studies in psoriasis with data from the prospective, multicenter BioCAPTURE cohort.
In **Chapter 8** one-year overall drug survival of adalimumab, etanercept and ustekinumab was described and compared after confounder-correction. Also, the one year drug survival of adalimumab, etanercept and ustekinumab (analyzed as one group) was combined with a quality of life measure (the DLQI). Combining drug survival with DLQI had not been done before.
In **Chapter 9** long-term (ten years) drug survival of adalimumab, etanercept and ustekinumab was presented. Overall drug survival, as well as drug survival split for discontinuation due to ineffectiveness and side-effects were assessed and compared after correction for confounders. This was unique in current literature. In this study we also analyzed the predictors for overall drug survival, and drug survival split for discontinuation due to ineffectiveness and side-effects. Research into predictors for discontinuation split for ineffectiveness and side-effects had only gained little attention. The few studies that addressed this issue had not been conducted with the same variables at start, leading to a heterogeneity in the selection of candidate predictors. In our study, we selected the candidate predictors from a set of baseline variables that was similar for every biologic. There was no drug survival study present in the literature in which this had been done before.

To explore

Research question 4: What is the long-term overall drug survival of adalimumab, etanercept, and ustekinumab in patients with psoriasis?

In **Chapter 8 and 9**, we showed that overall drug survival percentages of adalimumab, etanercept and ustekinumab were high in daily practice psoriasis treatment. In **Chapter 8**, overall drug survival rates were 74%, 68% and 85% with, respectively, adalimumab, etanercept and ustekinumab after one year of treatment. The study in **Chapter 9** is the most recent study. In this study, we showed that overall drug survival percentages of adalimumab, etanercept and ustekinumab were, respectively, 74.6%, 75.8% and 84% survival after one year and 41%, 34% and 61% survival after 5 years of treatment.

Overall drug survival percentages from a study by Inzinger *et al.* for adalimumab, etanercept and infliximab were, respectively, 70.9%, 70.8% and 58% after one year, and 47.5%, 44.6% and 11.7% after 5 years of treatment in patients with psoriasis.[2] In the study of Warren *et al.*, overall drug survival percentages in patients with psoriasis were 89% for ustekinumab, 79% for adalimumab, 70% for etanercept and 65% for infliximab after one year, and, respectively, 75%, 59%, 40% and 35% after 3 years of treatment.[36] The overall drug survival percentages after one and 5 years of treatment from our study are in line with the overall drug survival percentages from the studies of Inzinger *et al.* and Warren *et al.*

These drug survival percentages suggest that patients with psoriasis discontinue treatment less often with ustekinumab, compared with adalimumab, etanercept and infliximab, and this would make ustekinumab an interesting biologic for long-term treatment of psoriasis. However, in order to compare drug survival amongst biologics, correction for potential confounders has to be made, and this is described under research question 6.

Research question 5: Is drug survival accompanied with a good skin-specific quality of life in patients with psoriasis?

Since psoriasis is a skin disease with a high impact on the quality of life of patients, including a quality-of-life-indicator is important in order to evaluate treatment success with biologics. In **Chapter 8** we combined overall drug survival with the skin-specific quality of life questionnaire DLQI. From the patients with psoriasis that were still being treated with a biologic after a year, we saw that the percentage of patients with a good quality of life (defined as happy patients; those with a DLQI≤5) increased over time. Of patients, 27% was 'happy' at baseline and 79% was 'happy' at one year of biologic treatment. Limitations were that (1) at different time points, different patient groups were presented; (2) there were patients who were still being treated with a biologic, but did not return a DLQI questionnaire; and (3) there were patients that did not return a DLQI questionnaire because they already discontinued the biologic. However, there were no differences between the group that returned DLQI questionnaires and the group in which no DLQI questionnaires were returned. Also, DLQI questionnaires were missing at random time points, and therefore selection bias was less likely. Altogether, we have shown that there was a large increase in the percentage of patients with psoriasis with a good quality of life amongst those patients who stayed on treatment with biologics during the first year and returned a DLQI questionnaire. In addition, we have shown that a group of patients (21%) still has an impaired quality of life (DLQI>5) after one year of biologic treatment. It would be of interest to analyze why the DLQI in these patients remains > 5 despite the continuation of biologic treatment. By combining DLQI with drug survival, we have shown that biologics are of high value in the treatment of patients with psoriasis in daily practice.

The concept of 'happy' drug survival (drug survival combined with DLQI questionnaires) is new in the current literature. Therefore no other studies were available to compare our study with.

To compare

Research question 6: Which biologic has the highest confounder-corrected, long-term overall drug survival in patients with psoriasis?

Our daily practice study in **Chapter 8** showed that ustekinumab had the highest confounder-corrected, overall drug survival compared with etanercept and that there was a trend towards a better drug survival of ustekinumab compared with adalimumab after one year of treatment.

In **Chapter 9** we showed that the long-term (> 5 years) confounder-corrected, overall drug survival of ustekinumab was significantly higher compared with the long-term overall drug survival of adalimumab and etanercept. Thus, patients with psoriasis had significantly less chance to discontinue ustekinumab treatment for any reason, compared with adalimumab or etanercept.

Other prospective and retrospective daily practice studies showed similar results with ustekinumab having the highest confounder-corrected, long-term overall drug survival compared with the biologics adalimumab, etanercept and infliximab.[36-39] In two of these studies[36,37], ustekinumab had the highest confounder-corrected, overall drug survival of these four biologics in patients with psoriasis who started a biologic for the first time. Thus, when considering overall drug survival, ustekinumab is well-suited for long-term treatment of psoriasis in daily practice. Of note, drug survival can be influenced by external factors such as the number of available biologics after the current biologic (i.e., the number of choices left), and the decision of physicians and patients to consider a biologic to be "ineffective". The number of available biologics left is, however, not of influence on drug survival when the patients with psoriasis who received a biologic for the first time, are considered. Also in this group of patients, ustekinumab was superior to adalimumab, etanercept and infliximab.[34] In our BioCAPTURE cohort, infliximab was the last choice biologic, and therefore our results are not likely to be influenced by the number of available biologics left. The number of patients treated with infliximab was to low in our cohort to include infliximab into the analyses.

Although results are in favour of ustekinumab, other biologics are also important in the treatment of patients with psoriasis. The course of psoriasis varies between individuals, and individual patients with psoriasis have their own profile of comorbidities and comedication. Effectiveness and safety are both very important in long-term treatment with a biologic for sustained disease control. To be able to control disease for patients with these different profiles, it is important that treatments with different mechanisms of action and safety profiles are at the patients and doctors disposal.

Research question 7: Which biologic has the highest confounder-corrected, long-term drug survival split for reasons of discontinuation, i.e. ineffectiveness and side-effects, in patients with psoriasis?

Unique in our study in **Chapter 9** compared with other drug survival studies was the comparison of confounder-corrected drug survival of biologics split for reasons of discontinuation. We showed that long-term (> 5 years) confounder-corrected drug survival of ustekinumab was significantly higher compared with the long-term drug survival of adalimumab and etanercept, split for ineffectiveness as well as for side-effects as reasons for discontinuation. This means that ustekinumab during long-term treatment of patients with psoriasis, is significantly less often discontinued due to ineffectiveness or side-effects compared with adalimumab or etanercept.

The number of studies that split drug survival for reason of discontinuation is scarce. In psoriasis, two other prospective studies split drug survival, but did not correct for confounders. In these studies, patients with psoriasis discontinued treatment due to ineffectiveness most often with etanercept and due to side-effects most often with infliximab.[36,38]

To predict

Research question 8: What are the predictors of long-term overall drug survival of biologics in patients with psoriasis?

In **Chapter 9** we showed that the most important predictors for a shorter overall drug survival were a higher baseline BMI and female sex when the biologics adalimumab, etanercept and ustekinumab were analyzed as one group. In other words, patients with a higher BMI at start of treatment as well as female patients had a significantly higher chance of discontinuing outpatient biologic treatment. When only adalimumab was considered, no significant predictors were found for a shorter overall drug survival. In etanercept treatment, predictors for a shorter overall drug survival were higher baseline BMI, female sex and the presence of specific comorbidities (i.e., comorbidities that would have resulted in exclusion from participation in RCTs). In ustekinumab treatment, the predictor for a shorter overall drug survival was higher baseline BMI.

In prospective and retrospective drug survival studies in patients with psoriasis, a heterogeneity exists in the predictors for overall drug survival.[2,36-43] This heterogeneity can be explained by the selection of different (baseline) variables for analyzing the predictors. It is, however, remarkable that female sex is mentioned most often in these drug survival studies as a predictor for discontinuation in general (i.e., overall drug survival) of biologics in the treatment of patients with psoriasis.[2,36-38,40] Body Mass Index (or obesity) is also mentioned several times as a predictor for early discontinuation in general of biologics.[39,41,43]

Noteworthy, female sex is also frequently mentioned as reason for early discontinuation in general of biologic treatment in other indications with registered use for biologics.

Female sex is stated to predict shorter overall drug survival in studies of biologic treatment in patients with psoriatic arthritis[44,45], rheumatoid arthritis[46], and ankylosing spondylitis[47-51].

Research question 9: What are the predictors of long-term drug survival split for biologics and split for reasons of discontinuation, i.e. ineffectiveness and side- effects, in patients with psoriasis?

In our study in **Chapter 9**, we showed that a higher baseline BMI was a predictor for discontinuation of a biologic in patients with psoriasis due to ineffectiveness for adalimumab, etanercept, and ustekinumab as one group, and for etanercept and ustekinumab separately. For adalimumab, higher baseline BMI was not statistically significant.

Female sex was a predictor for discontinuation of a biologic due to side-effects for adalimumab, etanercept, and ustekinumab as one group, but was also a consistent predictor for adalimumab, etanercept and ustekinumeb separately.

The finding that in female patients the treatment with a biologic is more often discontinued due to side-effects compared with male patients, is intriguing. No specific patterns of side-effects that were a reason for ending biologic therapy in female patients were found in the studied cohort.

Although scarce, publications on this topic have demonstrated gender differences in the presentation of symptoms, prognosis of diseases and treatment outcomes as well as communication.[52] One prospective study found that, after correction for possible confounders, female patients compared with male patients experienced more adverse drug reactions to certain drugs, i.e. anti-inflammatory agents for the musculoskeletal system and antibacterials.[53] In another prospective study regarding hospital in-patients it was shown that severe adverse drug reactions were seen more often in women than in men.[54] Thus, it is possible that female patients experience more side-effects compared with male patients in general or to certain drugs.

In other indications, the number of studies assessing predictors for the different reasons of discontinuation of biologics is scarce. In patients with rheumatoid arthritis it was seen that female sex predicted early discontinuation of the biologic due to side-effects, but also due to ineffectiveness.[46] The number of studies in rheumatoid arthritis is, however, limited.[46]

Conclusions for drug survival

- Long-term drug survival of biologics for psoriasis treatment is high in daily practice.
- Drug survival is accompanied with a good quality of life in patients with psoriasis. At baseline, the percentage of patients with psoriasis on biologic treatment in daily practice that were 'happy' (i.e., DLQI≤5) was 27%. After 1 year of biologic treatment, the percentage of 'happy' patients increased to 79%.
- Ustekinumab has the highest confounder–corrected, long-term (> 5 years) overall drug survival in the treatment of psoriasis in daily practice, compared with adalimumab and etanercept.
- Ustekinumab, compared with adalimumab and etanercept, has the highest confounder-corrected, long-term drug survival split for discontinuation due to ineffectiveness as well for side-effects in psoriasis treatment in daily practice.
- Patients with psoriasis with a higher BMI at start of treatment as well as female patients have a significantly higher probability of discontinuing outpatient biologic treatment (i.e., adalimumab, etanercept and ustekinumab as one group).
- A higher baseline BMI predicts discontinuation due to ineffectiveness in patients with psoriasis treated with etanercept or ustekinumab in daily practice.
- Female sex predicts discontinuation due to side-effects in patients with psoriasis treated with adalimumab, etanercept or ustekinumab in daily practice.

Improvements of efficacy and effectiveness

To explore

Research question 10: What are the guidelines that dermatologists in the Netherlands should adhere to when treating patients with psoriasis in daily practice?

Until the moment of translating and publishing the Dutch guidelines on Psoriasis 2011 as described in **Chapter 10**, no Dutch guidelines on psoriasis treatment had been published in the international literature. A guideline was available in the Dutch Journal of Medicine (NTvG).[55]

Until then, guidelines on the treatment of psoriasis were already available from England, Germany, Europe and the United States in the international literature.[8,56-60] In contrast to these guidelines, the Dutch guidelines on psoriasis contain unique chapters on the treatment of psoriasis of the face and flexures, childhood psoriasis as well as the patient's perspective on treatment. These chapters were therefore of added value to the current literature. For the contents of the Dutch guidelines on Psoriasis 2011, the reader is referred to **Chapter 10**.

Information that is mostly lacking in almost all guidelines on the treatment of psoriasis, is the use of conventional systemic agents in combination with biologics or with other conventional systemic agents. A difference between the Dutch guidelines on Psoriasis 2011 and the German guidelines on psoriasis is the addition of the 'treatment goals' in the German guidelines. These treatment goals advise a physician when to consider treatment adjustment or switching to another treatment.[7] Both combination treatment as well as 'treatment goals' could improve the care of patients with psoriasis. In **Chapter 11** and **Chapter 12**, these subjects were highlighted and they will be discussed below.

Research question 11: Since information on systemic combination therapy is largely lacking in current guidelines on psoriasis treatment, what is the current evidence from RCTs on systemic combination treatment in psoriasis?

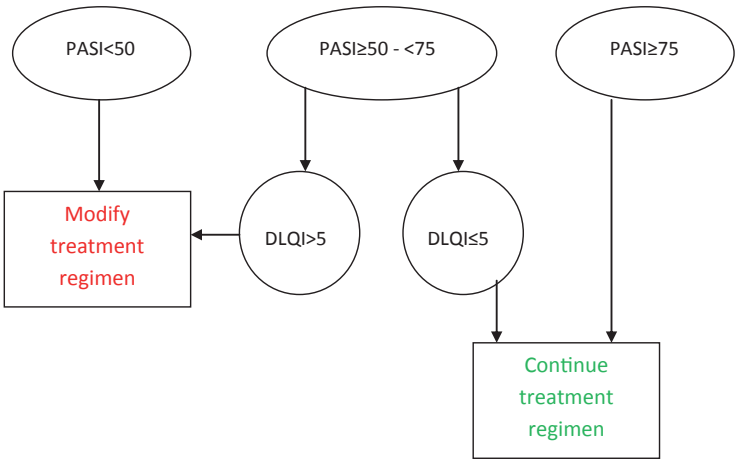
In **Chapter 11** we described our systematic review on the efficacy of systemic combination treatments in patients with psoriasis. The recently developed GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the level of evidence for different outcome measures from selected RCTs. A systematic review on the systemic combination treatments in psoriasis had, until then, not been performed using the GRADE method.

Eventually, 17 RCTs were included that described one of the following combination treatments: (1) phototherapy in combination with traditional systemic agents except acitretin, (2) phototherapy in combination with biologics, (3) biologics in combination with traditional systemic agents, and (4) combination of traditional systemic agents.

Phototherapy combined with acitretin was excluded from our systemic review because, for this type of combination therapy, an overview of RCT evidence according to the GRADE approach already existed in the NICE (National Institute for Health and Care Excellence) guidelines on psoriasis 2012.[59] The reader is referred to these NICE guidelines for the results on phototherapy combined with acitretin.
The evidence on the use of combination treatments in psoriasis is low. Best evidence currently exists for the superior efficacy of etanercept combined with methotrexate from start of treatment in the short-term compared with etanercept monotherapy.
Since dermatologists have to combine treatments in patients with psoriasis in daily practice[3], well-designed RCTs on the efficacy an safety of combination treatments are needed.

Research question 12: Do dermatologists already intuitively apply 'treatment goals' in patients with psoriasis treated with biologics in daily practice?
Treatment goals for psoriasis were drafted in 2011 (Figure 1). Treatment goals advise physicians that in patients with psoriasis in which a PASI50 has not been reached, treatment should be adjusted (e.g., dose increase, shortening of treatment interval, combination treatment with a topical or conventional systemic agent, or switching of treatment).[7,62-64] Physicians are advised to continue treatment in patients in which a PASI75 is reached during treatment. Physicians should use the DLQI questionnaire for patients that fall into the 'gray zone', i.e. with a PASI50 but not a PASI75 during

Figure 1 Treatment goals in psoriasis



Treatment goals in psoriasis. Figure adapted from Mrowietz, et al.[62]

treatment, in order to evaluate whether treatment should be continued or adjustments to treatment should be made.[62] In patients with a DLQI similar to or below 5 (good quality of life) treatment may be continued without modification, and a DLQI above 5 should lead to modification of treatment.[62]

These treatment goals are based on consensus. Formal study on the effect of treatment goals in daily practice is currently lacking. Treatment goals were evaluated with data from RCTs of adalimumab[65], although treatment goals have been made for daily practice.

In our study, described in **Chapter 12**, we used prospective data from the BioCAPTURE registry to evaluate whether dermatologists intuitively followed treatment goals, without the active implementation of treatment goals in daily practice. This had never been done before.

Our study showed that in 64% of the in total 395 analysed visits, dermatologists intuitively followed treatment goals. In 233 visits no treatment modification was necessary and therapy was indeed not modified in 194 (83%) of these visits. Noteworthy, of the 40 modifications that were performed in this group, 26 (65%) modifications were a dose decrease. Although this is not in accordance with the advice from the treatment goals, these changes are not as necessarily 'wrong'. Some modifications (7 out of 40 modifications) included a dose increase of biologics, although according to the treatment goals treatment should have been continued without modification.

In 103 (64%) of the 162 visits in which treatment should have been modified according to treatment goals, treatment was continued without modification. In this group of patients with a PASI<50 or a PASI50-<75 and a DLQI>5, most room for improvement of psoriasis care exists. In only 59 of 162 (26%) visits, treatment was indeed modified. Usually this was a dose increase of the biologic (24 of 61 modifications), or a switch to another biologic (11 of 61 modifications). The dose of the biologic or the conventional systemic agents was, however, also sometimes decreased (7 of 61 modifications; in which 1 modification of the biologic according to label). This type of modification was not according to treatment goals.

With our study we have shown that dermatologists intuitively followed treatment goals in the majority of visits, but that in a substantial number of visits in which the dermatologist should have modified treatment, treatment was continued without modification. Optimising treatment in this latter group of patients and exposing the barriers amongst dermatologists and patients for modifying treatment, as well as research into the implementation of treatment goals in daily practice could contribute to a higher effectiveness of biologic treatments in this group of patients.

A drawback of the current treatment goals is the use of a relative PASI score to base treatment decisions on. As shown in **Chapter 7** we advise to also use absolute PASI scores in the assessment of psoriasis severity. Treatment goals could therefore improve by adding absolute PASI measures.

A prospective study in which is evaluated whether the use of treatment goals contributes to an improvement of the treatment of patients with psoriasis, is needed before the (modified) treatment goals will be implemented in daily clinical practice. Especially a prospective, randomized study on the implementation of treatment goals as has been performed in patients with rheumatoid arthritis, could be of added value to the treatment of patients with psoriasis with biologics in daily practice.[66] The study in rheumatoid arthritis patients showed that implementation of treatment goals in daily practice led to improved disease activity and quality of life in patients, without additional costs.[66] A similar study in patients with psoriasis in daily practice could lead to a statement in future guidelines on psoriasis treatment to implement (modified) treatment goals in daily practice psoriasis care.

Conclusions for improvements of efficacy and effectiveness

- Combination therapy as well as use of (modified) treatment goals might improve the effectiveness of antipsoriatic treatments.
- Best evidence is available from RCTs for the combination therapy etanercept with methotrexate on short-term (12 weeks).
- Dermatologists intuitively followed treatment goals in the majority of visits in daily practice. However, in a substantial number of visits in which the dermatologist should have modified treatment, treatment was continued without modification. Optimising treatment in this group of patients with a response below PASI50 or a PASI50-<75 and a DLQI>5, and defining barriers amongst dermatologists and patients for modifying treatment, as well as research into the implementation of treatment goals in daily practice could contribute to a higher effectiveness of biologic treatments in this group of patients.

Short summary of important findings

In this thesis, we have shown that biologics and conventional systemic agents are effective for the treatment of psoriasis in daily practice. Of the biologics studied, ustekinumab showed superior effectiveness compared to etanercept during the first five years of treatment. During this five year period, ustekinumab was, compared with adalimumab and etanercept, most often prescribed in low to normal dose. Our drug survival studies revealed that ustekinumab had the highest confounder corrected overall drug survival compared to adalimumab and etanercept as well as the lowest discontinuation due to ineffectiveness as well as discontinuation due to side-effects. Ustekinumab is therefore an interesting biologic for long-term treatment of psoriasis.
Important predictors for treatment success (i.e. high clinical effectiveness at week 24 or long-term drug survival) of psoriasis with biologics were baseline BMI, baseline PASI score, and gender. Patients with a lower BMI at start of treatment had a higher chance of achieving PASI≤5 (and even PASI≤3) at week 24 and a higher probability of long-term drug survival compared to patients with higher baseline BMI. A higher baseline BMI predicted discontinuation due to ineffectiveness in patients with psoriasis treated with etanercept or ustekinumab. Male patients had a higher probability of long-term drug survival compared to female patients. Female gender predicted more frequent discontinuation due to side-effects in patients with psoriasis treated with adalimumab, etanercept or ustekinumab. Patients with a baseline PASI<10 had a higher chance of achieving PASI≤5 (and even PASI≤3) at week 24 compared to patients with PASI≥10. Of these predictors, BMI is modifyable and might become of high value in improving treatment outcome in daily practice psoriasis treatment.
Other strategies to improve treatment outcome with biologics in daily practice might include the use of combination therapy (i.e. the combination of a biologic with a conventional systemic agent) and the use of (modified) treatment goals to identify those patients in need of treatment modification.

Future directions

Future research in the treatment of psoriasis on the main themes effectiveness, drug survival and targeted treatment are essential for improving psoriasis care.

Although the PASI score is the most widely used measure in efficacy and effectiveness of antipsoriatic treatments, other measures are also being used, leading to a heterogeneity in outcomes for efficacy/effectiveness. This makes comparison of efficacy/effectiveness amongst studies difficult. Also, the time point at which PASI is assessed varies across studies, making comparisons even more of a challenge. Having multiple outcome measure could also potentially lead to different predictors for different outcomes. Hence, an international consensus is needed on the primary endpoint of efficacy/effectiveness and the time point of evaluation of short- and long-term treatment, analogues to what is being performed in eczema (HOME initiative).[67] Support from the international psoriasis community is needed to achieve the use of these outcome measures worldwide.

We showed that the number of comparative studies in psoriasis treatment is scarce. There is a need for long-term daily practice studies that compare the biologics as well as studies that compare the conventional systemic agents, with correction for confounders and accounting for doses. Comparative randomized studies could provide insight into a hierarchy of antipsoriatic treatments, complemented with studies from daily practice. Pragmatic randomized daily practice studies could provide physicians long-term data on comparative effectiveness of anti-psoriatic agents.[68]

We also showed that obesity might have an influence on effectiveness results of biologic treatments for psoriasis. A well-designed randomized (daily practice) study is needed, in which the effect of weight loss in patients with psoriasis treated with biologics (adalimumab, etanercept, infliximab, ustekinumab and secukinumab) is assessed. Performing such a study is a challenge. For example, patients with psoriasis treated with biologics could be randomized into a group with diet and physical exercise with a personal trainer and a group without the intervention. A blinded assessor would assess the PASI score at baseline and at several predefined time-points during the study. A questionnaire on adherence with biologic treatment has to be implemented into the study. Treatment adherence could be a confounder, since a higher adherence might be expected in the intervention group. In this study, also pro- and anti-inflammatory cytokines that are being produced by the adipose tissue, such as TNF-α, IL-6, leptin, and adiponectin, should be measured in serum at several time points during the study. In order to circumvent the problem for the biologics that are being administered based on weight (infliximab, ustekinumab), the first study could include only those biologics that have a fixed dose (adalimumab, etanercept and secukinumab). Future studies could also address BMI-based dosing.

With our BioCAPTURE cohort, we have shown that BMI is a predictor for discontinuation due to ineffectiveness for etanercept and ustekinumab, and that female sex is a predictor for discontinuation due to side-effects. These results should be replicated in larger, multicenter, prospective daily practice studies.

Observational studies are needed into why female patients are more prone to discontinuing biologic treatment in psoriasis due to side-effects, and whether in general female patients discontinue medication more often than male patients and the reasons for this sex difference.

Targeted treatment could arise from assessing predictors such as patient characteristics (e.g., obesity, female sex), but also from other biomarkers such as genetics. At the moment, BioCAPTURE is gathering information on biomarkers in order to evaluate the possibilities of patient-targeted treatment.

Treatment of biologics in psoriasis could be improved by information on the effect of combination therapy of conventional systemic agents with biologics. Currently, best evidence exists only for the combination etanercept with methotrexate and only on short-term treatment (12 weeks). More RCTs are needed on the short- and long-term efficacy (and safety) of combination therapy of biologics with conventional systemic agents. At the moment, the randomized multicenter study OPTIMAP (OPTIMising Adalimumab treatment in Psoriasis with concomitant methotrexate) is being conducted in order to compare adalimumab monotherapy with the combination of adalimumab with low dose methotrexate.

Improving treatment outcome might also be done by increasing biologic dose. More studies are needed to evaluate whether dose increase of biologics is indeed an effective measure in daily practice psoriasis treatment and to identify which patients with psoriasis benefit from such a dose increase. Of note, dose decreases are also of interest in that it might lead to successful treatment with biologics but with lower costs. Currently, we are conducting the randomized, multicenter study CONDOR (CONtrolled DOse Reduction), in which we assess the controlled decrease of biologic dose in psoriasis treatment.

Implementing treatment goals into daily practice might improve the prescription of biologics with dose adjustments and combination treatments for the group of patients in which PASI score is not sufficiently low enough. However, treatment goals should first be modified, so that decisions on treatment adjustments are not based (solely) on relative PASI measure as a first step of evaluation, but also on absolute PASI measures. Subsequently, the implementation of a modified treatment goals algorithm could then be evaluated in a randomized study, analogous to the randomized study (TICORA) in rheumatoid arthritis.[66]

References

1 Garcia-Doval I, Carretero G, Vanaclocha F et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Archives of dermatology 2012; 148: 463-70.

2 Inzinger M, Wippel-Slupetzky K, Weger W et al. Survival and Effectiveness of Tumour Necrosis Factor-alpha Inhibitors in the Treatment of Plaque Psoriasis under Daily Life Conditions: Report from the Psoriasis Registry Austria. Acta dermato-venereologica 2015.

3 Zweegers J, Otero ME, van den Reek JM et al. Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review. Acta dermato-venereologica 2016; 96: 453-8.

4 Kothary N, Diak IL, Brinker A et al. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. Journal of the American Academy of Dermatology 2011; 65: 546-51.

5 Driessen RJ, Berends MA, Boezeman JB et al. Psoriasis treatment with etanercept and efalizumab: clinical strategies influencing treatment outcome. The British journal of dermatology 2008; 158: 1098-106.

6 Zweegers J, de Jong EM, Nijsten TE et al. Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology. Dermatology online journal 2014; 20.

7 Nast A, Boehncke WH, Mrowietz U et al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 2012; 10 Suppl 2: S1-95.

8 Pathirana D, Ormerod AD, Saiag P et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV 2009; 23 Suppl 2: 1-70.

9 Van Lumig PP, Driessen RJ, Boezeman JB et al. Long-term efficacy of etanercept for psoriasis in daily practice. The British journal of dermatology 2012; 166: 445-7.

10 van Lumig PP, van de Kerkhof PC, Boezeman JB et al. Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naive vs. non-naive patients. Journal of the European Academy of Dermatology and Venereology : JEADV 2013; 27: 593-600.

11 de Groot M, Appelman M, Spuls PI et al. Initial experience with routine administration of etanercept in psoriasis. The British journal of dermatology 2006; 155: 808-14.

12 Strober BE, Bissonnette R, Fiorentino D et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). Journal of the American Academy of Dermatology 2016.

13 Puig L, López A, Vilarrasa E, et al. Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 1633-53.

14 Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. British journal of dermatology 2015; 172: 504-12.

15 Nestle FO, Kaplan DH, Barker J. Psoriasis. The New England journal of medicine 2009; 361: 496-509.

16 Krueger JG, Ferris LK, Menter A et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. The Journal of allergy and clinical immunology 2015; 136: 116-24 e7.

17 Goffe B, Cather JC. Etanercept: An overview. Journal of the American Academy of Dermatology 2003; 49: S105-11.

18 Bain B, Brazil M. Adalimumab. Nature reviews. Drug discovery 2003; 2: 693-94.

19 Talamonti M, Botti E, Galluzzo M et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. The British journal of dermatology 2013; 169: 458-63.

20 Talamonti M, Galluzzo M, Chimenti S et al. HLA-C*06 and response to ustekinumab in Caucasian patients with psoriasis: Outcome and long-term follow-up. Journal of the American Academy of Dermatology 2016; 74: 374-5.

21 van den Reek JM, van Lumig PP, Kievit W et al. Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice. The Journal of dermatological treatment 2013; 24: 361-8.
22 Cassano N, Loconsole F, Miracapillo A et al. Treatment of psoriasis with different dosage regimens of etanercept: preliminary results from the Talpharanta Plastic Study Group. International journal of immunopathology and pharmacology 2010; 23: 797-802.
23 Gisondi P, Cotena C, Tessari G et al. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. Journal of the European Academy of Dermatology and Venereology : JEADV 2008; 22: 341-4.
24 Naldi L, Addis A, Chimenti S et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. Dermatology (Basel, Switzerland) 2008; 217: 365-73.
25 Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25: 1007-11.
26 Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert opinion on biological therapy 2014; 14: 749-56.
27 Naldi L, Conti A, Cazzaniga S et al. Diet and physical exercise in psoriasis: a randomized controlled trial. The British journal of dermatology 2014; 170: 634-42.
28 Upala S, Sanguankeo A. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. International journal of obesity (2005) 2015; 39: 1197-202.
29 Edson-Heredia E, Sterling KL, Alatorre CI et al. Heterogeneity of response to biologic treatment: perspective for psoriasis. The Journal of investigative dermatology 2014; 134: 18-23.
30 Gremese E, Tolusso B, Gigante MR et al. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Frontiers in immunology 2014; 5: 576.
31 Gremese E, Carletto A, Padovan M et al. Obesity and reduction of the response rate to anti-tumor necrosis factor alpha in rheumatoid arthritis: an approach to a personalized medicine. Arthritis care & research 2013; 65: 94-100.
32 Maas F, Arends S, van der Veer E et al. Obesity Is Common in Axial Spondyloarthritis and Is Associated with Poor Clinical Outcome. The Journal of rheumatology 2016; 43: 383-7.
33 di Minno MN, Peluso R, Iervolino S et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis care & research 2013; 65: 141-7.
34 Bhalme M, Sharma A, Keld R et al. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? European journal of gastroenterology & hepatology 2013; 25: 543-9.
35 Versini M, Jeandel PY, Rosenthal E et al. Obesity in autoimmune diseases: not a passive bystander. Autoimmunity reviews 2014; 13: 981-1000.
36 Warren RB, Smith CH, Yiu ZZ et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). The Journal of investigative dermatology 2015.
37 Menter A, Papp KA, Gooderham M et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). Journal of the European Academy of Dermatology and Venereology : JEADV 2016.
38 Gniadecki R, Bang B, Bryld LE et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. The British journal of dermatology 2015; 172: 244-52.
39 Vilarrasa E, Notario J, Bordas X et al. ORBIT (Outcome and Retention Rate of Biologic Treatments for Psoriasis): A retrospective observational study on biologic drug survival in daily practice. Journal of the American Academy of Dermatology 2016.
40 Esposito M, Gisondi P, Cassano N et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. The British journal of dermatology 2013; 169: 666-72.

41 Spertino J, Lopez-Ferrer A, Vilarrasa E et al. Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. Journal of the European Academy of Dermatology and Venereology : JEADV 2014; 28: 1514-21.
42 Puig L, Ruiz-Salas V. Long-term efficacy, safety and drug survival of ustekinumab in a Spanish cohort of patients with moderate to severe plaque psoriasis. Dermatology (Basel, Switzerland) 2015; 230: 46-54.
43 Di Lernia V, Tasin L, Pellicano R et al. Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis. The Journal of dermatological treatment 2012; 23: 404-9.
44 Iannone F, Lopriore S, Bucci R et al. Two-year survival rates of anti-TNF-alpha therapy in psoriatic arthritis (PsA) patients with either polyarticular or oligoarticular PsA. Scandinavian journal of rheumatology 2015; 44: 192-9.
45 Glintborg B, Ostergaard M, Dreyer L et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: results from the nationwide Danish DANBIO registry. Arthritis and rheumatism 2011; 63: 382-90.
46 Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology 2016; 55: 523-34.
47 Lorenzin M, Ortolan A, Frallonardo P et al. Predictors of response and drug survival in ankylosing spondylitis patients treated with infliximab. BMC musculoskeletal disorders 2015; 16: 166.
48 Gulfe A, Kapetanovic MC, Kristensen LE. Efficacy and drug survival of anti-tumour necrosis factor-alpha therapies in patients with non-radiographic axial spondyloarthritis: an observational cohort study from Southern Sweden. Scandinavian journal of rheumatology 2014; 43: 493-7.
49 Glintborg B, Ostergaard M, Krogh NS et al. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Annals of the rheumatic diseases 2010; 69: 2002-8.
50 Heinonen AV, Aaltonen KJ, Joensuu JT et al. Effectiveness and Drug Survival of TNF Inhibitors in the Treatment of Ankylosing Spondylitis: A Prospective Cohort Study. The Journal of rheumatology 2015; 42: 2339-46.
51 Fafa BP, Louzada-Junior P, Titton DC et al. Drug survival and causes of discontinuation of the first anti-TNF in ankylosing spondylitis compared with rheumatoid arthritis: analysis from BIOBADABRASIL. Clinical rheumatology 2015; 34: 921-7.
52 Teunissen TA, Rotink ME, Lagro-Janssen AL. Gender differences in quality of care experiences during hospital stay: A contribution to patient-centered healthcare for both men and women. Patient education and counseling 2016; 99: 631-7.
53 Zopf Y, Rabe C, Neubert A et al. Gender-based differences in drug prescription: relation to adverse drug reactions. Pharmacology 2009; 84: 333-9.
54 Davies EC, Green CF, Taylor S et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PloS one 2009; 4: e4439.
55 Spuls PI, Tuut MK, van Everdingen JJ et al. [The practice guideline 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis']. Nederlands tijdschrift voor geneeskunde 2004; 148: 2121-5.
56 Smith CH, Anstey AV, Barker JN et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. The British journal of dermatology 2005; 153: 486-97.
57 Smith CH, Anstey AV, Barker JN et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. The British journal of dermatology 2009; 161: 987-1019.
58 Nast A, Kopp I, Augustin M et al. German evidence-based guidelines for the treatment of Psoriasis vulgaris (short version). Archives of dermatological research 2007; 299: 111-38.
59 Nast A, Boehncke WH, Mrowietz U et al. German S3-guidelines on the treatment of psoriasis vulgaris (short version). Archives of dermatological research 2012; 304: 87-113.
60 Menter A, Gottlieb A, Feldman SR et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Journal of the American Academy of Dermatology 2008; 58: 826-50.
61 National Institute for Health and Care Excellence. About NICE guidance. http://www.nice.org.uk/guidance. Accessed May 2016.

62 Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Archives of dermatological research 2011; 303: 1-10.
63 Mrowietz U, Kragballe K, Nast A et al. Strategies for improving the quality of care in psoriasis with the use of treatment goals--a report on an implementation meeting. Journal of the European Academy of Dermatology and Venereology : JEADV 2011; 25 Suppl 3: 1-13.
64 Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2012; 26 Suppl 2: 12-20.
65 Mrowietz U, Kragballe K, Reich K et al. An assessment of adalimumab efficacy in three Phase III clinical trials using the European Consensus Programme criteria for psoriasis treatment goals. The British journal of dermatology 2013; 168: 374-80.
66 Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004; 364: 263-9.
67 Schmitt J, Spuls PI, Thomas KS *et al.* The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *The Journal of allergy and clinical immunology* 2014; **134**: 800-7.
68 Williams HC, Burden-Teh E, Nunn AJ. What is a pragmatic clinical trial? J Invest Dermatol. 2015 Jun;135 (6): e33.

14

Nederlandse Samenvatting

Nederlandse Samenvatting

In Nederland hebben ongeveer 500.000 personen de huidziekte psoriasis, waarvan ± ⅓ matig-ernstige tot ernstige psoriasis heeft. Psoriasis gaat gepaard met een grote impact op de kwaliteit van leven. Het verbeteren van de zorg en het optimaliseren van de behandeling van patiënten met psoriasis is een continu proces waarbij wetenschappelijk onderzoek essentieel is.

Een van de nieuwste generatie behandelingsopties van matig-ernstige tot ernstige psoriasis zijn de biologics. Biologics zijn medicijnen die vervaardigd zijn via levende organismen, en die specifiek aangrijpen op cellen van het immuunsysteem. Adalimumab, etanercept en infliximab grijpen aan op tumor necrose factor (TNF)-α en ustekinumab grijpt aan op interleukine (IL)-12 en IL-23. Infliximab en ustekinumab worden, in tegenstelling tot adalimumab en etanercept, gedoseerd op het gewicht van de patiënt.

Het doel van dit proefschrift was het exploreren, vergelijken en voorspellen van de effectiviteit van biologics voor psoriasis in de dagelijkse praktijk, het exploreren van drug survival (een samengestelde maat voor behandelsucces, dat wil zeggen effectiviteit, veiligheid, en gedrag van de patiënt en van de arts), het vergelijken en voorspellen van lange termijn drug survival en het exploreren van gebieden met ruimte voor verbetering in de behandeling van psoriasis in de dagelijkse praktijk.

De studies in dit proefschrift zijn gebaseerd op data uit de literatuur en afkomstig uit BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use REgistry with Biologics). BioCAPTURE is een prospectief, multicenter cohort van patiënten met matig tot ernstige psoriasis die behandeld worden met biologics. Data over effectiviteit, veiligheid, patiënt gerapporteerde uitkomstmaten en kosten-effectiviteit worden verzameld. BioCAPTURE is gesitueerd in het Radboudumc Nijmegen en is opgezet in 2005. Vanaf 2010 participeren grote regionale ziekenhuizen in BioCAPTURE, met op het moment negen regionale centra. BioCAPTURE bevat dus data van academische en niet-academische ziekenhuizen.

Data afkomstig uit dagelijkse praktijk cohorten zijn belangrijk en relevant en een aanvulling op data uit gerandomiseerde klinische studies (RCTs) doordat in dagelijkse praktijk studies (1) grotere aantallen patiënten geïncludeerd kunnen worden met andere patiëntkarakteristieken dan de patiënten in RCTs, (2) patiënten gedurende een langere tijd gevolgd kunnen worden, (3) behandelstrategieën verschillen met de strategieën in RCTs, (4) veiligheid van medicatie goed kan worden vastgesteld door de inclusie van grotere aantallen patiënten en een langere follow-up tijd dan in RCTs, en (5) het gedrag van artsen en patiënten geëvalueerd kan worden.

In dit hoofdstuk worden de resultaten van **hoofdstuk 5 – 12** samengevat.

Effectiviteit

Exploreren

Hoofdstuk 5 beschrijft de eerste systematische review waarin de effectiviteit van biologics (adalimumab, etanercept, infliximab, ustekinumab) en conventionele systemische medicatie (acitretine, cyclosporine, fumaarzuur, methotrexaat) voor de behandeling van psoriasis geaggregeerd werd op basis van data uit dagelijkse praktijk studies. Wij zagen dat zowel biologics als conventionele systemische medicatie effectief waren in de behandeling van psoriasis in de dagelijkse praktijk. Opvallend was dat de meeste studies geen goede beschrijving gaven van bepaalde belangrijke patiënt-karakteristieken bij start ('baseline') van de behandeling, alsmede geen goede beschrijving gaven van (het effect van) dosisophoging en het voorschrijven van conventionele systemische medicatie in combinatie met biologics. Ook ontbraken goed uitgevoerde studies waarin de effectiviteit van systemische antipsoriatische medicatie onderling vergeleken werd bij de behandeling van psoriasis in de dagelijkse praktijk.

Vergelijken

In **hoofdstuk 6** beschreven we de eerste dagelijkse praktijk studie waarin de lange termijn (5 jaars) effectiviteit door middel van de PASI (Psoriasis Area and Severity Index) score werd vergeleken tussen de meest gebruikte biologics adalimumab, etanercept en ustekinumab bij patiënten met psoriasis, waarbij gecorrigeerd werd voor mogelijke verstorende variabelen ('confounders'). We hielden rekening met (1) de dosering van de biologic, (2) combinatietherapieën van een biologic met een conventioneel systemisch medicament, en (3) verschillen in baseline patiënten-karakteristieken bij start met een biologic, zoals verschillen in baseline PASI scores. De primaire uitkomst was het vergelijken van het gemiddelde PASI verloop tussen de biologics gedurende de eerste 5 jaar van psoriasis behandeling. We zagen dat ustekinumab, vergeleken met etanercept, significant effectiever was in het verlagen van de PASI score gedurende de periode van 5 jaar behandeling van psoriasis in de dagelijkse praktijk. Ook was ustekinumab, vergeleken met adalimumab en etanercept, de biologic die het vaakst in een dosering werd voorgeschreven die in overeenstemming was met of lager was dan de verwachte label dosering gedurende deze 5 jaar in ons cohort. De andere biologics werden vaker in een hogere dosering dan wat verwacht mocht worden volgens label dosering voorgeschreven. Dit maakt ustekinumab aantrekkelijk voor lange termijn behandeling van patiënten met psoriasis.

Voorspellen

Met de studie in **hoofdstuk 7** analyseerden we het percentage van behandelepi-soden met een hoge respons en voorspellers voor een hoge respons op biologic

therapie bij psoriasis op week 24 van de behandeling. Hoge respons werd gedefinieerd als een PASI90 (90% reductie in de PASI score ten opzichte van de baseline PASI score), PASI100 of een absolute PASI≤5, met in een van de sensitiviteits-analyses PASI≤3. Om de power te verhogen analyseerden we de biologics (adalimumab, etanercept, infliximab en ustekinumab) als één groep. We zagen een laag percentage PASI90 (15%) en PASI100 (3%) op week 24 van de biologic behandeling bij psoriasis. Een absolute PASI≤5 (59%) en zelfs een PASI≤2 (24%) werden vaker bereikt dan PASI90 op week 24. Dit toont het belang aan van het includeren van een absolute PASI score bij de beoordeling van de ernst van de psoriasis.
Als voorspeller voor PASI90 op week 24 vonden we een baseline PASI≥10, en voor PASI≤5 op week 24 vonden we een baseline PASI<10 en een lage baseline BMI (body mass index). Patiënten met psoriasis met een hogere baseline PASI (PASI≥10) hadden dus meer kans om een PASI90 te halen op week 24 dan patiënten met een lage baseline PASI score (PASI<10), en patiënten met psoriasis met een lage baseline PASI score hadden meer kans om een PASI≤5 en zelfs een PASI≤3 te halen op week 24 dan patiënten met een hoge baseline PASI score. Ook patiënten met psoriasis met een lagere BMI bij start van de behandeling hadden meer kans op het behalen van een PASI≤5 en zelfs een PASI≤3 op week 24 dan patiënten met een hogere baseline BMI. Van deze predictoren is baseline BMI een modificeerbare voorspeller. Patiënten zouden kunnen afvallen voordat zij starten met een biologic. De huidige studies in de literatuur zijn nog van onvoldoende kwaliteit om te kunnen stellen dat gewichtsverlies leidt tot een betere respons op biologic therapie bij psoriasis in de dagelijkse praktijk. Er zijn additionele studies nodig om dit te analyseren. Daarnaast bestaat de vraag of we moeten gaan toewerken naar op BMI gebaseerde biologic doseringen.

Drug survival

Drug survival bij de behandeling met biologics is de kans (waarschijnlijkheid) dat een patiënt nog steeds behandeld wordt met een biologic na een bepaalde periode. Een drug survival curve kan gemaakt worden voor verschillende redenen van stop. Redenen voor het stoppen van de biologic kunnen zijn ineffectiviteit, bijwerkingen, zwangerschapswens, of andere redenen zoals de wens van de patiënt. Bij 'overall' drug survival worden alle redenen van stop meegenomen in de analyse. Drug survival kan ook gesplitst worden voor de belangrijkste redenen van stop: ineffectiviteit en bijwerkingen.
We hebben twee drug survival studies uitgevoerd voor psoriasis met data uit de prospectieve, multicenter BioCAPTURE.

Exploreren

In **hoofstuk 8** zagen we drug survival percentages van 74%, 68% en 85% voor respectievelijk adalimumab, etanercept en ustekinumab na één jaar biologic behandeling bij psoriasis. In **hoofdstuk 9** zagen we voor adalimumab, etanercept en ustekinumab respectievelijk drug survival percentages van 74.6%, 75.8% en 84% na één jaar behandeling en 41%, 34% en 61% na een periode van 5 jaar behandeling. Deze lange termijn drug survival percentages zijn hoog in de dagelijkse praktijk en komen overeen met de percentages uit andere studies. De hoogste percentages worden gezien voor ustekinumab. In **hoofdstuk 8** hebben we de drug survival over een periode van één jaar gekoppeld aan de kwaliteit van leven van de patiënt met behulp van de DLQI (Dermatology Life Quality Index) vragenlijst. Dit was nog nooit eerder gedaan. We zagen een toename in het percentage patiënten met een goede DLQI, gedefinieerd als een DLQI≤5, met op baseline 27% van de patiënten met een DLQI≤5 en na één jaar behandeling 79% van de patiënten met een DLQI≤5. Door het combineren van drug survival met DLQI hebben we laten zien dat biologics van grote waarde zijn voor de behandeling van patiënten met psoriasis in de dagelijkse praktijk. Wat we hiermee ook getoond hebben, is dat er patiënten zijn (21%) die na een jaar biologic behandeling alsnog een beperkte kwaliteit van leven hebben (DLQI>5). Er is dus ruimte voor verbetering en onderzoek is nodig naar de reden van een DLQI > 5 bij deze groep patiënten ondanks langdurige behandeling met biologics.

Vergelijken

In **hoofdstuk 8** toonden we dat ustekinumab de hoogste confounder-gecorrigeerde, overall drug survival heeft vergeleken met etanercept en dat er een trend was voor een betere drug survival van ustekinumab ten opzichte van adalimumab in de behandeling van psoriasis na een periode van één jaar. In **hoofdstuk 9** lieten we zien dat ustekinumab de hoogste confounder-gecorrigeerde, overall drug survival heeft vergeleken met adalimumab en etanercept na een periode van >5 jaar behandeling van patiënten met psoriasis. Psoriasis patiënten die behandeld werden met ustekinumab hadden dus op de lange termijn minder kans om te stoppen met deze biologic dan patiënten die behandeld werden met adalimumab of etanercept. In **hoofdstuk 9** voerden we als eersten de confounder-gecorrigeerde analyses uit voor drug survival opgeplitst voor redenen van stop. We toonden dat ustekinumab de hoogste confounder-gecorrigeerde drug survival heeft voor de stopreden 'ineffectiviteit' én voor de stopreden 'bijwerkingen' vergeleken met adalimumab en etanercept na een periode van >5 jaar behandeling van patiënten met psoriasis. Patiënten met psoriasis die behandeld werden met ustekinumab hadden dus minder kans om te stoppen met deze biologic ten gevolge van ineffectiviteit of bijwerkingen dan patiënten met psoriasis die behandeld werden met adalimumab of etanercept, gekeken over een periode van >5 jaar behandeling.

Hoewel deze vergelijkende studies in het voordeel zijn voor ustekinumab als biologic in de behandeling van psoriasis patiënten in de dagelijkse praktijk, willen we als kanttekening maken dat andere biologics ook belangrijk blijven in de behandeling van psoriasis. Elke patiënt heeft zijn/haar eigen psoriasis en zijn/haar eigen profiel van comorbiditeiten en comedicatie, en daarom zijn biologics met verschillende werkingsmechanismen en veiligheidsprofielen nodig om de individuele patiënt zo goed mogelijk te kunnen behandelen.

Voorspellen

Tot het uitvoeren van onze studie in **hoofdstuk 9** had het voorspellen van drug survival nog maar weinig aandacht gekregen en hadden de onderzoekers die deze studies uitvoerden gebruik gemaakt van een heterogene set aan baseline variabelen om de drug survival te voorspellen. Dit resulteerde in een heterogene set aan predictoren (voorspellers) voor de verschillende biologics. In onze studie hebben we binnen één cohort de voorspellers vastgesteld voor overall drug survival en de drug survival gesplitst voor ineffectiviteit en voor bijwerkingen door gebruik te maken van dezelfde baseline variabelen voor elke analyse. Wij analyseerden daarbij de biologics adalimumab, etanercept en ustekinumab als één groep, maar ook afzonderlijk in de behandeling van psoriasis.

Wij toonden aan dat een hogere BMI bij de start van behandeling en het vrouwelijk geslacht voorspellers waren voor het eerder stoppen met een biologic behandeling (adalimumab, etanercept en ustekinumab als één groep geanalyseerd) voor patiënten met psoriasis in de dagelijkse praktijk. Bij opsplitsen van drug survival naar redenen van stop lieten we zien dat een hogere baseline BMI een voorspeller was voor het eerder stoppen met etanercept of ustekinumab met als stopreden 'ineffectiviteit'. Het vrouwelijk geslacht was een consistente voorspeller voor het eerder stoppen van adalimumab, etanercept of ustekinumab ten gevolge van bijwerkingen.

Grotere prospectieve cohorten zijn nodig om onze predictoren te bevestigen. Verder zijn, zoals reeds eerder gesteld, additionele studies nodig naar de invloed van gewichtsreductie op de effectiviteit van biologic behandeling. Eveneens interessant is de vraag waarom vrouwelijke patiënten met psoriasis meer kans hebben om de biologic behandeling te stoppen in verband met bijwerkingen. Observationele studies zijn nodig om dit te analyseren en om uit te zoeken of vrouwen in het algemeen vaker stoppen met medicijnen dan mannen en wat de reden is van dit geslachtsverschil.

Het verbeteren van de effectiviteit

Exploreren

Met **hoofdstuk 10** hebben we de Nederlandse richtlijn voor de behandeling van patiënten met psoriasis gepubliceerd in de internationale literatuur. In tegenstelling tot andere richtlijnen die al aanwezig waren in deze literatuur beslaat de Nederlandse richtlijn unieke hoofdstukken over de behandeling van psoriasis van het gelaat en de lichaamsplooien, psoriasis op de kinderleeftijd en het patiëntenperspectief op de behandeling.

In bijna alle huidige richtlijnen ontbreekt informatie over combinatietherapie van conventionele systemische medicatie met biologics of met andere conventionele systemische medicatie. De Duitse richtlijn heeft als toevoeging de behandeldoelen ('treatment goals') voor psoriasis. Zowel combinatietherapie als behandeldoelen kunnen de zorg van patiënten met psoriasis verbeteren. In **hoofdstuk 11** en **hoofdstuk 12** hebben we deze onderwerpen belicht en we zullen ze hieronder kort bespreken.

In **hoofdstuk 11** beschreven we een systematisch review over de effectiviteit van systemische combinatietherapieën bij patiënten met psoriasis en gebruikten daarbij de GRADE (Grading of Recommendations Assessment, Development and Evaluation) methode om de mate van bewijs vast te stellen voor verschillende uitkomstmaten van de geselecteerde RCTs. Een systematisch review over systemische combinatietherapieën in psoriasis gebruik makend van de GRADE methode was tot dan toe nog niet uitgevoerd. De geselecteerde RCTs over combinatietherapieën hadden over het algemeen een laag niveau van bewijs. Op dit moment bestaat het beste bewijs voor een superieure effectiviteit van etanercept gecombineerd met methotrexaat vanaf start van de behandeling vergeleken met etanercept monotherapie na 12 weken behandeling.

In **hoofdstuk 12** voerden we voor het eerst een studie uit waarbij de behandeldoelen voor psoriasis, zonder voorafgaande implementatie van deze behandeldoelen, geëvalueerd werden met prospectief verzamelde data uit BioCAPTURE betreffende de dagelijkse praktijk behandeling van psoriasis. We zagen dat dermatologen intuïtief de behandeldoelen volgden in het merendeel van de visites in de dagelijkse praktijk. Echter in een substantieel deel van de visites zagen we ook dat dermatologen de behandeling voor patiënten met psoriasis hadden moeten aanpassen volgens de behandeldoelen, maar dat de huidige behandeling van de patiënt gecontinueerd werd zonder modificaties. Met name in de groep met een PASI<50 of met een PASI50-<75 en een DLQI>5 is winst te behalen. Het optimaliseren van de behandeling van patiënten met een respons onder de PASI50 of met een PASI50-<75 en een DLQI>5, en het onderzoeken van barrières onder dermatologen en patiënten om de behandeling aan te passen, evenals onderzoek naar de implementatie van behandeldoelen in

de dagelijkse praktijk zou kunnen leiden tot een hogere effectiviteit van biologic behandelingen in deze groep patiënten.

PART VI

ABOUT THE AUTHOR

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Curriculum Vitae

Curriculum Vitae

Jeffrey Zweegers werd geboren op 29 januari 1987 in Eindhoven. In 2005 behaalde hij zijn Gymnasiumdiploma aan het Pleincollege Sint-Joris te Eindhoven, waarna hij de studie Geneeskunde startte aan de Radboud Universiteit Nijmegen.
Na het behalen van het Masterdiploma Geneeskunde eind 2011, volgden in 2012 werkzaamheden als arts-onderzoeker bij de Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV) te Utrecht, in samenwerking met de afdelingen Dermatologie van het Radboudumc te Nijmegen en het AMC te Amsterdam, en daarmee het begin van zijn promotietraject.
In mei 2013 startte hij als arts-onderzoeker Dermatologie in het Radboudumc te Nijmegen om vervolg te geven aan zijn promotietraject met behulp van data afkomstig uit BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use REgistry with Biologics). Gedurende ruim drie jaar voerde hij werkzaamheden uit op het gespecialiseerde spreekuur voor biologics op de afdeling Dermatologie van het Radboudumc te Nijmegen en was hij als subinvestigator betrokken bij verschillende fase 3 en fase 4 studies.
Gedurende zijn promotie werd hij begeleid door Prof. Dr. E.M.G.J. de Jong, Prof. Dr. Dr. P.C.M. van de Kerkhof en Dr. W. Kievit verbonden aan het Radboudumc te Nijmegen en Prof. Dr. Ph.I. Spuls verbonden aan het AMC te Amsterdam.
In januari 2016 startte hij als arts in opleiding tot specialist (AIOS) op de afdeling Dermatologie in het Radboudumc te Nijmegen. Jeffrey is getrouwd met Frazima Zweegers-Mukamurenzi op 15 mei 2015. Samen hebben zij een zoon Samuel en wonen ze in Nijmegen.

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List of publications

List of publications

1. **Frequency of and predictors for a high clinical response in psoriasis patients on biologic therapy in daily practice.**
   Results from the prospective, multicenter BioCAPTURE cohort.
   Zweegers J, Roosenboom B, van de Kerkhof PC, van den Reek JM, Otero ME, Atalay S, Kuijpers AL, Koetsier MI, Arnold WP, Berends M, Weppner-Parren L, Bijen M, Njoo MD, Mommers JM, van Lümig PP, Driessen RJ, Kievit W, De Jong EM.
   Br J Dermatol. 2017 Mar; 176(3): 786-93.

2. **Comparison of the one and 5-years effectiveness of adalimumab, etanercept and ustekinumab in psoriasis patients in daily clinical practice.**
   Results from the prospective BioCAPTURE registry.
   Zweegers J, Groenewoud JM, van den Reek JM, Otero ME, van de Kerkhof PC, Driessen RJ, van Lümig PP, Njoo MD, Ossenkoppele PM, Mommers JM, Koetsier MI, Arnold WP, Andriessen MP, Kuijpers AL, Berends MA, Kievit W, De Jong EM.
   Br J Dermatol. 2017 Apr; 176(4):1001-9.

3. **Comment on: "Review of patient registries in dermatology".**
   Zweegers J, Bronckers IM, van den Reek JM, van Geel MJ, van de Kerkhof PC, Seyger MM, de Jong EM.
   J Am Acad Dermatol. 2016 Dec;75(6):e241.

4. **Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in psoriasis patients treated with adalimumab, etanercept or ustekinumab in daily practice.**
   A prospective, comparative, long-term drug survival study from the BioCAPTURE registry.
   Zweegers J, van den Reek JM, van de Kerkhof PC, Otero ME, Kuijpers AL, Koetsier MI, Arnold WP, Berends M, Weppner-Parren L, Ossenkoppele PM, Njoo MD, Mommers JM, van Lümig PP, Driessen RJ, Kievit W, De Jong EM.
   Br J Dermatol. 2016 Aug;175(2):340-7.

5. **Effectiveness of biologic and conventional systemic therapies in adults with chronic plaque psoriasis in daily practice: a systematic review.**
   Zweegers J, Otero ME, van den Reek JM, van Lümig PP, Driessen RJ, Kievit W, Seyger MM, van de Kerkhof PC, De Jong EM.
   Acta Derm Venereol. 2016 May;96(4):453-8.

6. **Drug Survival Studies in Dermatology: Principles, Purposes, and Pitfalls.**
van den Reek JM, Kievit W, Gniadecki R, Goeman JJ, Zweegers J, van de Kerkhof PC, Seyger MM, de Jong EM.
J Invest Dermatol. 2015 Jul;135(7):e34.

7. **Polymorphisms in CD84, IL12B and TNFAIP3 are associated with response to biologics in patients with psoriasis.**
van den Reek JM, Coenen MJ, van de L'Isle Arias M, Zweegers J, Rodijk-Olthuis D, Schalkwijk J, Vermeulen SH, Joosten I, van de Kerkhof PC, Seyger MM, Zeeuwen PL, de Jong EM.
Br J Dermatol. 2017 May;176(5):1288-96.

8. **Predictors of adalimumab drug survival in psoriasis differ by reason for discontinuation: long-term results from the Bio-CAPTURE registry.**
van den Reek JM, Tummers M, Zweegers J, Seyger MM, van Lümig PP, Driessen RJ, van de Kerkhof PC, Kievit W, de Jong EM.
J Eur Acad Dermatol Venereol. 2015 Mar;29(3):560-5.

9. **Combined use of systemic agents for psoriasis: a systematic review.**
Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI.
JAMA Dermatol. 2014 Nov;150(11):1213-20.

10. **Comparing treatment goals of psoriasis with treatment decisions in daily practice.**
Results from a prospective cohort of patients with psoriasis treated with biologics: BioCAPTURE.
Zweegers J, van den Reek JM, van de Kerkhof PC, Otero ME, Ossenkoppele PM, Njoo MD, Mommers JM, Koetsier MI, Arnold WP, Sybrandy-Fleuren BA, Kuijpers AL, Andriessen MP, Kievit W, De Jong EM.
Br J Dermatol. 2014 Nov;171(5):1091-8.

11. **'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care.**
Results from the BioCAPTURE network.
van den Reek JM, Zweegers J, Kievit W, Otero ME, van Lümig PP, Driessen RJ, Ossenkoppele PM, Njoo MD, Mommers JM, Koetsier MI, Arnold WP, Sybrandy-Fleuren BA, Kuijpers AL, Andriessen MP, van de Kerkhof PC, Seyger MM, de Jong EM.
Br J Dermatol. 2014 Nov;171(5):1189-96.

12. **Summary of the Dutch S3-Guidelines on the treatment of psoriasis 2011. Dutch Society of Dermatology and Venereology.**
Zweegers J, de Jong EM, Nijsten TE, de Bes J, te Booij M, Borgonjen RJ, van Cranenburgh OD, van Deutekom H, van Everdingen JJ, de Groot M, van Hees CL, Hulshuizen H, Koek MB, de Kort WJ, de Korte J, Lecluse LL, Pasch MC, Poblete-Gutiérrez PA, Prens EP, Seyger MM, Thio HB, Torcque LA, de Vries AC, van de Kerkhof PC, Spuls PI.
Dermatol Online J. 2014 Mar 17; 20(3).

13. **Satisfaction of treatment with biologics is high in psoriasis.**
Results from the BioCAPTURE network.
van den Reek JM, van Lümig PP, Otero ME, Zweegers J, van de Kerkhof PC, Ossenkoppele PM, Njoo MD, Mommers JM, Koetsier MI, Arnold WP, Sybrandy-Fleuren BA, Kuijpers AL, Andriessen MP, Seyger MM, Kievit W, de Jong EM.
Br J Dermatol. 2014 May;170(5):1158-65.

14. **Parental experiences with propranolol versus oral corticosteroids for complicated infantile hemangioma, a retrospective questionnaire study.**
Hermans DJ, Zweegers J, Evers AW, van der Vleuten CJ.
Eur J Dermatol. 2013 Nov-Dec;23(6):857-63.

15. **Acitretin-induced transverse leukonychia.**
Zweegers J, Bovenschen HJ.
Int J Dermatol. 2014 Mar;53(3):e221-2.

16. **Propranolol in a case series of 174 patients with complicated infantile haemangioma: indications, safety and future directions.**
Hermans DJ, Bauland CG, Zweegers J, van Beynum IM, van der Vleuten CJ.
Br J Dermatol. 2013 Apr;168(4):837-43.

17. **Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice.**
van den Reek JM, van Lümig PP, Kievit W, Zweegers J, van de Kerkhof PC, Seyger MM, de Jong EM.
J Dermatolog Treat. 2013 Oct;24(5):361-8.

18. **A woman with skin abnormalities around the mouth.**
Zweegers J, Bovenschen HJ.
Ned Tijdschr Geneeskd. (NTvG) 2012;156:A461.

19. **The psychosocial impact of an infantile haemangioma on children and their parents.**
    Zweegers J, van der Vleuten CJ.
    Arch Dis Child. 2012 Oct;97(10):922-6.

20. **Sweet syndroom gelokaliseerd in een met radiotherapie behandelde huid.**
    Smits T, Zweegers J, Kuijpers AL.
    Nederlands Tijdschrift voor Dermatologie & Venereologie (NTvDV) 2012 Mei; 22(5):305-7.

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Dankwoord

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"Fall down seven times, get up eight" (Denzel Washington)